CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214958Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates
Version: 2018-01-24

Date:	September 8, 2022
Reviewer(s):	Xi Wang, PhD, MPH Division of Epidemiology I
Team Leader:	Benjamin Booth, PhD, MS Division of Epidemiology I
Division Director:	CAPT Sukhminder K. Sandhu, PhD, MPH, MS Division of Epidemiology I
Subject:	ARIA Sufficiency Memo for Pregnancy Safety Concerns
Drug Name(s):	Deucravacitinib
Application Type/Number:	NDA 214958
Applicant/sponsor:	Bristol Myers Squibb
OSE RCM #:	2021-1816

Expedited ARIA Sufficiency Template for Pregnancy Safety Concerns

1. BACKGROUND INFORMATION

1.1. Medical Product

Deucravacitinib is a selective tyrosine kinase 2 (TYK2) inhibitor indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.[1] Deucravacitinib is not recommended in patients with severe hepatic impairment (Child-Pugh C). The proposed recommended dosage is 6 mg orally once daily, with or without food.

1.2. Describe the Safety Concern

The Division of Dermatology and Dentistry (DDD) requested that the Division of Epidemiology (DEPI) assess the sufficiency of ARIA for broad-based safety signal detection studies among women exposed to deucravacitinib during pregnancy.

Safety during pregnancy due to drug exposure is a concern for women who are pregnant or of childbearing potential. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.[2]

Psoriasis occurs in 1% of female of reproductive potential, and therefore exposures, both intended and unintended, to deucravacitinib during pregnancy are anticipated. Clinical studies provide insufficient information about the safety of deucravacitinib when used during pregnancy. As of March 10, 2022, clinical data are available for the use of deucravacitinib in 13 pregnant women and pregnancy outcomes include live births (n=3, all reported as full-term infants; two cases reported first trimester exposure), elective terminations (n=4), spontaneous abortions (n=2), ectopic pregnancy (n=1), ongoing cases (n=2), and unknown outcome (n=1). No congenital malformations and perinatal complications were reported. Eleven additional pregnancies were reported in partners of male subjects exposed to deucravacitinib (7 live births, 1 elective termination, and 3 unknown outcomes).[3,4]

Sponsor proposed labeling for deucravacitinib has the following information regarding pregnancy.[5]

(b) (4)

[redacted]

[1] SOTYKTU label as of August 25, 2022. \\CDSESUB1\evsprod\nda214958\0046\m1\us\bms-25aug2022-init-nda-pso-deucr-pro.pdf.
[2] Dinatale M. Division of Pediatric and Maternal Health, FDA. The pregnancy and lactation labeling rule (PLLR). https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM520454.pdf. Accessed August 9, 2022.
[3] Applicant's March 22, 2022 IR response, page 16. \\CDSESUB1\evsprod\nda214958\0013\m1\us\2022-03-11-bms986165-response-fda-pv-q1-q2.pdf.
[4] Limpert J. Division of Pediatric and Maternal Health Review: deucravacitinib NDA 214958, Pregnancy and Lactation Labeling, April 22, 2022, DARRTS Reference ID: 4970998.
[5] See footnote 1

(b) (4)

[redacted]

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected

☐ No approved indication, but practitioners may use product off-label in pregnant women

☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized

☒ No approved indication, but use in pregnant women or women of child bearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision

and certainty

☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty. †

☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). †

† ***If checked, please complete General ARIA Sufficiency Template***

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☒ Pregnancy registry with internal comparison group
☐ Pregnancy registry with external comparison group
☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
☐ Electronic database study with chart review
☒ Electronic database study without chart review
☒ Other, please specify: Alternative study designs would be considered: e.g. retrospective cohort study using claims or electronic medical record data or a case-control study

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☐ Study Population
☐ Exposures
☒ Outcomes
☐ Covariates
☒ Analytical Tools

For any checked boxes above, please describe briefly:

Outcomes: ARIA lacks access to medical records; the prospective registry requires clinical information from medical records and risk factors that may not be available in claims data. The pregnancy registry being considered requires that an expert clinical geneticist or dysmorphologist review and classify medical records of all major congenital malformations. The study using claims or electronic medical data may be algorithm-based, if it shows an imbalance in any of the outcomes being investigated, FDA may consider requiring outcome validation in the selected database(s) or a chart-confirmed analysis.

Analytical tools: The required PMRs target more than one outcome, including major malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth. The required ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been fully implemented in post marketing surveillance for maternal and fetal outcomes.

2.5. Please include the proposed PMR language in the approval letter.

Two PMRs related to pregnancy outcomes were issued:[6]

1. Conduct a prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to deucravacitinib during pregnancy to an unexposed control population. The registry should be designed to detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

   For more information, see the May 2019 FDA draft guidance for Industry *Post approval Pregnancy Safety Studies* available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postapprovalpregnancy-safetystudies-guidance-industry

2. Conduct an additional pregnancy study that uses a different design from the pregnancy registry (for example a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to deucravacitinib during pregnancy compared to an unexposed control population.

[6] Oussova T, Postmarketing Requirements (PMR), deucravacitinib, NDA 214958, September 8, 2022, DARRTS Reference ID: 5042379.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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COA Tracking ID: C2021427
NDA Number/Referenced IND Number: 214958/131993

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA Tracking ID:	C2021427
NDA # / Referenced IND:	214958 / 131993
Applicant:	Bristol Myers Squibb
Established Name/Trade Name:	deucravacitinib (BMS-986165) tablets
Indication:	Treatment of moderate to severe plaque psoriasis
PDUFA Goal Date:	September 10, 2022
Review Division:	Division of Dermatology and Dentistry
Clinical Reviewer	Mary Joy Mejia
Clinical Team Leader (TL)	Amy Woitach
Regulatory Project Manager:	Jennifer Harmon
COA Reviewer:	Yasmin Choudhry, M.D.
COA TL:	Selena Daniels, PharmD, PhD
COA Director:	David Reasner, PhD
Instruments reviewed:	1. Psoriasis Symptoms and Signs Diary ☒ Patient-reported outcome (PRO)

Table of Contents

1. EXECUTIVE SUMMARY

In this submission, the applicant is seeking approval of deucravacitinib tablets for the treatment of adults with moderate to severe plaque psoriasis. The specific COA related labeling claims are related to complete symptom resolution which are derived from two multicenter randomized, double-blind, placebo- and active comparator-controlled phase 3 clinical trials (Studies IM011046 and IM011047). The primary objective of this review is to evaluate from a COA

perspective if the submitted information supports the COA-related labeling claims related to the concept(s) of interest.

The secondary efficacy patient-reported outcome (PRO) endpoint proposed for labeling is:

- Proportion of subjects who achieve a Psoriasis Symptoms and Signs Diary (PSSD) Symptom domain score of 0 among subjects with a baseline PSSD Symptom domain score ≥1

The data from Studies IM011-046 and -047 demonstrated:

- Deucravacitinib tablets had statistically significant improvement in the selected secondary efficacy endpoint compared with placebo.
- Deucravacitinib tablets had statistically insignificant improvement in the selected secondary efficacy endpoint compared to apremilast (active comparator).

From a COA perspective, the PSSD Symptom domain and its corresponding endpoint adequately support labeling claims.

2 REVIEW CONCLUSIONS

The content validity and other measurement properties of the PSSD were previously reviewed in BLA 761061 (guselkumab)[1]. The PSSD Symptom domain is adequate to support labeling claims.

Review Summary

- The PSSD Symptom domain measures important aspects of plaque psoriasis.
- The applicant has established content validity and the other measurement properties for the PSSD Symptom domain. This instrument has also been previously labeled in a similar development program.

Assessment of Study Endpoints

- The PSSD Symptom domain-based endpoint assesses clinical benefit via the targeted response of complete resolution of symptoms; this endpoint appears to adequately support labeling claims.

3 BACKGROUND AND CORRESPONDENCE ON CLINICAL OUTCOME ASSESSMENT(S)

Regulatory Background:
There has been previous communication regarding the PSSD for this development program during the IND stage (IND 131993), which included:

- Type B Meeting Minutes dated June 21, 2018:
  - Recommended the use of raw scores to enhance data interpretability.
  - Recommended using patient global rating anchor scales in addition to investigator global rating scales if deriving thresholds for meaningful change for the PSSD.

[1] COA review: C2016280_BLA 761061_Choudhry dated April 8, 2017 [DARRTS Reference ID: 4079858]

- Recommended using an electronic device with a reminder or alarm function.

Disease Background:
Psoriasis, a prototypic IL-23 mediated disease, characterized mostly by erythematous, well-demarcated, scaly plaques on the skin. Psoriasis can involve skin in any part of the body; particularly disabling is the involvement of specific anatomic regions, such as hands and feet (palmoplantar), face, scalp, and nails. Commonly reported symptoms of plaque psoriasis include itch, pain, stinging, burning, and skin tightness.

Investigational Product:
Deucravacitinib (DEUC) is an oral, selective tyrosine kinase 2 (TYK2) inhibitor. TYK2 is an intracellular non-receptor kinase that mediates the signaling of the pro-inflammatory cytokines interleukin (IL)-23, IL-12, and Type I interferons (IFN). IL-23, IL-12, and type I IFNs are naturally occurring cytokines that are upregulated in inflammatory and immune responses.

Materials Reviewed:
The materials reviewed for this submission are listed in Table 1 (shown on next page).

Table 1. Materials reviewed

Document	**SDN**	**eCTD#**	**Date Received**
5.3.5.1 Studies IMO 11046 and 11047, Appendix 9.2 PRO Report Psoriasis Symptoms and Sign Diary (PSSD) Supplemental Statistical Analysis Report	1	0001	10 Sept 2021
1.11.3 Clinical Information Amendment: Response to FDA Information Request dated 16-Mar-2022	16	0016	5 April 2022
Communications and Reviews	**DARRTS Ref ID**		**Date**
Type B Meeting Minutes	4281161		21 June 2018
Previous COA Review: C2018044_IND 131993_Choudhry	4240029		5 April 2018
Previous COA Review: C2016280_BLA 761061_Choudhry	4079858		8 April 2017

Reviewer's comment(s): *The PSSD Supplemental statistical analysis report was intended to provide supportive evidence to aid the interpretation of the analyses of differences in PSSD Symptoms domain mean change that was conducted as part of the primary clinical analyses in both Studies IM011-046 and -047. Note: A full evidence dossier was not included in this submission.*

4 CLINICAL OUTCOME ASSESSMENT REVIEW

4.1 Clinical Trial Population

The target population for Studies IM011-046 and -047 were adults who had moderate to severe plaque psoriasis (defined as Psoriasis Area Severity Index (PASI) score ≥ 12, static Physician's Global Assessment (sPGA) ≥ 3, and body surface area involvement ≥10% at both Screening Visit and Day 1). Participants were required to have stable plaque psoriasis (defined as no morphology changes or significant flares of plaque psoriasis in the opinion of the investigator) for 6 months or more. To be eligible, subjects also had to be deemed a candidate for phototherapy or systemic therapy by the investigator.

A complete list of the inclusion and exclusion criteria is summarized in clinical study protocols IM011046 and IM011047.

Reviewer's comment(s): *While not specified as an inclusion criterion, participants who had PSSD Symptom domain scores ≥ 1 at baseline were included in both studies (IM011046 and IM011047).*

4.2 Clinical Trial Design

Studies IM011-046 and -047 were 52-week, multi-center, randomized, double-blind, double-dummy, placebo- and active comparator-controlled phase 3 studies to compare the efficacy and safety of deucravacitinib 6mg once daily (QD) versus placebo and apremilast 30 mg twice daily (BID) in subjects with moderate to severe plaque psoriasis.

Studies IM011-046 and -047 were similar in design; however, Study IM011-047 included randomized withdrawal and retreatment periods.

Patients who completed the screening procedures and met the inclusion/exclusion criteria were randomized on Day 1 in a 2:1:1 ratio, respectively, to one of the following three treatment arms:

- Deucravacitinib 6 mg QD
- Placebo
- Apremilast titrated to 30 mg BID

For Study IM011-046, 965 subjects were screened, 666 subjects were randomized, and 665 subjects were treated. For Study IM011-047, 1519 subjects were enrolled, 1020 subjects were randomized, and 1018 subjects were treated.

Refer to the clinical study reports for more details regarding the trial design for Studies IM011-046 and -047.

4.3 Endpoint Position, Definition, and Assessment Schedule

The study endpoints for Studies IM011-046 and -047 are as follows:

Co-primary efficacy endpoints:

- Proportion of subjects who achieve an sPGA score of 0 or 1 with at least a 2-point improvement at Week 16 from baseline.
- Proportion of subjects who achieve a 75% improvement in PASI score at Week 16 from baseline.

Secondary efficacy COA endpoints (multiplicity adjusted):

- Proportion of subjects who achieve a PSSD Symptom domain score of 0 among subjects with a baseline PSSD Symptom domain score ≥1 at Week 16. (compared to placebo)
- Change from baseline in PSSD symptom score at Week 16. (compared to apremilast)
- Proportion of subjects who achieve a PSSD Symptom domain score of 0 among subjects with baseline PSSD Symptom domain score ≥ 1 at Week 16. (compared to apremilast)

PSSD data was collected via an electronic device. The PSDD was administered daily from baseline to Week 52. For Study IM011-046, > 90% of participants completed the PSSD at Baseline and 75.6% to 78.9% of participants completed the PSSD at Week 16. For Study IM011-047, > 90% of participants completed the PSSD at Baseline and 72 to 79% of participants completed the PSSD at Week 16.

Reviewer's comment(s): *Most participants completed the PSSD for analysis of the secondary efficacy COA endpoint. Participants continued to complete the PSSD for the remainder of the study:*

Study IM011-046: 72.6% to 77.1% of participants completed the PSSD at Week 24, and 65.7% to 73.6% of participants completed the PSSD at Week 52.

Study IM011-047: 69.7% to 74.6% of participants completed the PSSD at Week 24. This Study continued till Week 52 however, the completion rates for Week 52 were not included in the PSSD supplemental statistical analysis report.

4.4 Targeted Clinical Outcome Assessment-Related Labeling Claim(s)

The applicant has proposed the following specific targeted COA-related labeling claims (in *blue italicized* text):

Patient Reported Outcomes
A greater proportion of patients treated with [TRADENAME] compared to placebo achieved Psoriasis Symptoms and Signs Diary (PSSD) symptom score of 0 (absence of itch, pain, burning, stinging, and skin tightness) at Week 16.

Reviewer's comment(s):
The PSSD Symptom domain appears to adequately support labeling claims for the following reasons:

- *The PSSD Symptom domain measures important aspects of plaque psoriasis.*

- *The applicant has established content validity and the other measurement properties for the PSSD Symptom domain. This instrument has also been previously labeled in another development program (BLA 761061; guselkumab).*

To ensure that the data included in the proposed label was not false or misleading, an information request was submitted on March 11,2022 requesting PSSD item distributions by response categories and item-level descriptive statistics. Upon review of the applicant's response (SDN 16 received April 5, 2022), this reviewer noted the following:

- *The item-level baseline PSSD Symptom scores and distributions of response were generally similar between treatment groups (DEUC and placebo).*
- *There were no significant (≥ 15%) floor or ceiling effects in the lowest (0) and highest (10) response categories for the PSSD Symptom items (i.e., itch, pain, stinging, burning, and skin tightness).*
- *There was no single item overly influencing the Symptom domain score; the item-level change from baseline PSSD Symptom domain scores showed consistent trends.*

5 CLINICAL OUTCOME ASSESSMENT(S)

5.1 Clinical Outcome Assessment Description(s)

Psoriasis Symptoms and Signs Diary (PSSD)

The PSSD is an 11-item PRO instrument designed to assess the severity of symptoms and signs of plaque psoriasis. It consists of two domains: Symptom (itch, pain, stinging, burning, and skin tightness) and Sign (skin dryness, cracking, scaling, shedding or flaking, redness, bleeding). Each item is rated on an 11-point numeric rating scale ranging from 0 ("Absent") to 10 ("Worst imaginable"). There are two different recall versions of the PSSD: 24-hour and 7-day. The 24-hour recall version is the subject of this review.

5.2 Conceptual Framework(s)

The conceptual framework for the PSSD is shown in Table 2.

Table 2. Conceptual Framework for PSSD

Item	Domain	General Concept
Item 1: *Itch*	Symptom	Plaque psoriasis symptoms and sign severity
Item 2: *Pain*		
Item 3: *Stinging*		
Item 4: *Burning*		
Item 5: *Skin tightness*		
Item 6: *Dryness*	Sign	
Item 7: *Cracking*		
Item 8: *Scaling*		
Item 9: *Shedding or flaking*		
Item 10: *Redness*		
Item 11: *Bleeding*		

5.3 Scoring Algorithm

PSSD

The PSSD generates domain and total scores. This section will focus on the Symptom domain score as it is the subject of this review. The PSSD Symptom domain score is derived by averaging the five symptom items (i.e., itch, pain, stinging, burning, and skin tightness) and multiplying by 10. The PSSD Symptom domain score has a possible range of 0 to 100, where 0 represents the least severe symptom and 100 represents the most severe symptom.

To obtain a symptom score on a given day, responses to at least 2 of the 5 questions must be available. If more than 3 questions were missing, the symptom score was considered to be missing.

To calculate the scores at each visit, the daily scores with 24-hour recall periods over the prior 7 days were used and the average score to each of the 11 questions was used as the score at that visit. In case missing data arose during the 7 days prior to the visit, daily scores of at least 4 days out of the 7 days were used. If greater than 3 days of the 7 were missing, the average score was set to missing. The baseline PSSD Symptom domain scores was calculated based on the daily diary data collected during the screening period.

5.4 Content Validity

The applicant conducted a literature review/landscape review to inform the selection of the PSSD. A summary of the literature review/landscape review is below.

Literature review/Landscape review

The applicant reviewed several streams of information to understand and document what are relevant and important symptoms to subjects with moderate to severe plaque psoriasis, including:

- Voice of the Patient Report based on the Patient-Focused Drug Development (PFDD) Meeting on Psoriasis[2] held on March 17, 2016
- Published qualitative evidence from the development of the PSSD[3,4]
- Ongoing confirmatory literature review being completed by BMS.

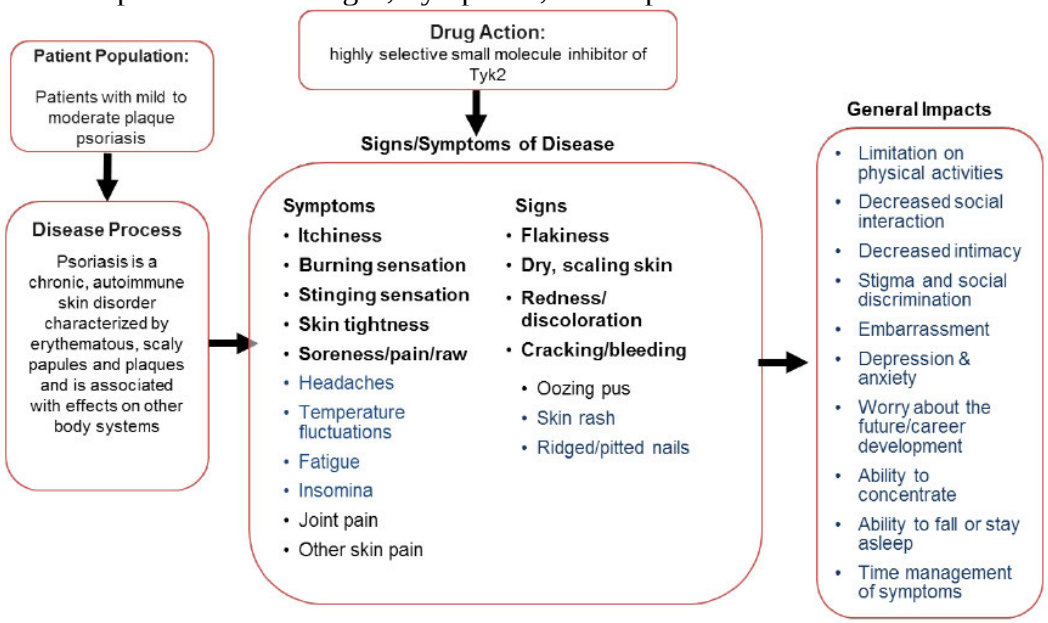
The Psoriasis Voice of the Patient report identified the following symptoms that have the most significant impact on subjects' daily lives: itching, pain or soreness, burning or stinging and the following subject-observed signs: flakiness, dry scaly skin, redness/discoloration, cracking/bleeding.

Based on the review of information, the applicant created a conceptual model (Figure 1; shown on next page) that highlights the most proximal, relevant, and important symptoms, signs, and impacts in plaque psoriasis.

2 FDA Center for Drug Evaluation and Research. The Voice of the Patient: Psoriasis. 2016.
3 Feldman SR. Development of a patient-reported outcome questionnaire for use in adults with moderate-to-severe plaque psoriasis: The Psoriasis Symptoms and Signs Diary. Journal of Dermatology & Dermatologic Surgery 2017;20:19–26.
4 Mathias SD. Measurement properties of a patient-reported outcome measure assessing psoriasis severity: The psoriasis symptoms and signs diary. Journal of Dermatological Treatment 2016;27:4, 322-327.

The applicant also conducted a landscape review to identify existing PRO assessments that have been used to evaluate symptoms and signs in psoriasis. Three PRO assessments were identified: Psoriasis Symptom Inventory (PSI), Psoriasis Symptom Diary (PSD), and PSSD. The applicant concluded that the PSSD was the only instrument that included patient observable signs (e.g., flakiness, dry scaling skin, redness/ discoloration and cracking/bleeding). As such, the applicant decided to carry forward with the PSSD for their phase 3 development program.

Figure 1. Conceptual Model of Signs, Symptoms, and Impacts in Moderate to Severe Psoriasis



The applicant documented the development activities that were conducted for the PSSD by the original developers, which included a literature review, expert input and patient interviews. Per the applicant, the developers of the PSSD began with a literature review and engaged clinical experts (including (b) (4)) to provide input into the development of items for the PSSD. The applicant provided a summary of the completed qualitative research based on Feldman et al., 2016 which is presented below. Refer to the previous COA review (C2016280_BLA 761061_Choudhry dated April 8, 2017) for more details regarding the content validity of the PSSD.

Patient Interviews

Face-to-face, one-on-one concept elicitation (CE) semi-structured interviews were conducted with 20 patients in the United States with moderate to severe plaque psoriasis to better understand symptoms and impacts experienced by individuals with psoriasis.

Based on the CE data, items were generated to form a draft version of the PSSD. This was tested

in cognitive debriefing interviews (in three waves) with patients to evaluate the patients' understanding of the content, clarity, and relevance of the two versions of the draft PSSD. Ten interviews were conducted in the first wave, four in the second, and five in the third. During the final wave, patients had no issues and indicated the final 11-item version was clear and comprehensive.

Additionally, after cognitive interviews were completed, a confirmatory round of concept elicitation interviews with five patients was performed to ensure the final scale was adequate and comprehensive. These five patients were asked to describe symptoms and signs they experienced because of their psoriasis on a typical day. The most frequent symptoms and signs mentioned were the same as those reported by subjects in the initial concept elicitation interviews, and were already included in the PSSD: redness, itching, flaking, pain, scaling, and bleeding.

The frequency of symptoms and signs mentioned by the interview participants are shown in Table 3.

Table 3. Frequency of Symptoms and Signs Mentioned

	Initial Concept Elicitation Interviews (n=20)	Cognitive Interviews (n=19)	Final Concept Elicitation Interviews (n=5)
Symptom	**n (%)**		
Itchiness	17 (85)	16 (84)	5 (100)
Soreness/pain/raw	16 (80)	14 (74)	3 (60)
Flakiness	15 (75)	11 (58)	3 (60)
Dry, scaly skin	14 (70)	13 (68)	3 (60)
Redness/discoloration	14 (70)	10 (53)	5 (100)
Hot/burning/stinging sensation	12 (60)	14 (74)	1 (20)
Cracking/bleeding	10 (50)	13 (68)	2 (40)
Joint pain *	3 (15)	7 (37)	1 (20)
Skin tightness	2 (10)	16 (84)	0 (0)
Oozing pus	1 (5)	0 (0)	0 (0)

*Joint pain was removed as a key concept as it was mostly associated with psoriatic arthritis

Reviewer's comment(s):
Based on the review of the qualitative study report submitted in BLA 761061, the majority of the concepts included in the PSSD (itch, redness, scaling, burning, stinging, cracking, flaking, pain, and skin tightness) are relevant and important to patients with plaque psoriasis. These concepts are also consistent with previous literature and patient input from the PFDD meeting.

The PSSD (24-hour recall version) was translated and culturally adapted in accordance to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)[5] principles

[5] Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, Erikson P; ISPOR Task Force for Translation and Cultural Adaptation. Principles of Good Practice for the Translation and Cultural Adaptation

McKown et al. (2020)[6] for the translation and cultural adaptation process. The PSSD has been translated in the following languages: Australia-English, Canada-English, Canada-French, Czech Republic-Czech, Germany-German, UK-English, Hungary-Hungarian, Poland-Polish, Russia-Russian, South Korea-Korean, Spain-Spanish, Taiwan-Chinese, and USA-Spanish.

5.5 Other Measurement Properties

The applicant documented the psychometric evaluation of the PSSD by the original developers. The PSSD was psychometrically evaluated using the following sources:

- 2-week non-interventional study in adult patients (>18 years) with moderate to severe plaque psoriasis (n=106)
- Multicenter, randomized, double-blind phase 3 studies in adult patients (>18 years) to evaluate the efficacy and safety of guselkumab in patients with moderate to severe plaque psoriasis compared with placebo and adalimumab (n=871)

Refer to the previous COA review (C2016280_BLA 761061_Choudhry dated April 8, 2017) for more details regarding the design of these studies. Note that the phase 3 studies were used to only assess responsiveness and score interpretability of the PSSD-7day recall version, as such this section will focus on the psychometric findings from the non-interventional study as the PSSD-24h version is the subject of this review.

The applicant provided a summary of the completed psychometric evaluation which is presented in the following section. Refer to the previous COA review (C2016280_BLA 761061_Choudhry dated April 8, 2017) for more details regarding the other measurement properties of the PSSD.

Reviewer's comment(s): *The trial population used in the guselkumab development program appears to be consistent with the trial population for Studies IM011-046 and -047.*

5.5.1 Non-Interventional Study

Item Characteristics

Descriptive analyses of individual item responses revealed that severity scores were relatively symmetrically distributed. In the PSSD-24h, some floor effects were present for the symptoms of burning (31%), stinging (26%) and pain (26%) indicating that that burning, stinging, and pain might not be experienced by most patients. However, scale-level analysis of PSSD-24h Symptom Scores did not exhibit ceiling or floor effects.

Reliability

- For assessment of test-retest reliability[7], the intraclass correlation coefficients (ICCs) for all PSSD-24h scales were ≥ 0.80 at weeks 1 and 2.

Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. Value Health. 2005 Mar-Apr;8(2):94-104.

[6] McKown S, Acquadro C, Anfray C, et al. Good practices for the translation, cultural adaptation, and linguistic validation of clinician-reported outcome, observer-reported outcome, and performance outcome measures. J Patient Rep Outcomes. 2020;4(1):89.

7 Stability was defined as respondents who indicated no change from baseline based on body surface area.

- For assessment of internal consistency reliability, Cronbach's alpha coefficient was ≥0.960 for the PSSD-24h.

Construct Validity

- For assessment of known-groups validity, participants in the most severe disease group[8] produced the highest PSSD symptom and sign severity scores. The subjects' PSSD Symptom and Sign Scores were approximately 45 in the most severe disease groups based on the PASI, PGI, and DLQI groupings. The PSSD Symptom and Sign Score were much lower in the least severe groups and ranged from approximately 15-25.
- For assessment of convergent validity, the PSSD-24h was moderately-to-strongly correlated with reference measures (e.g., 36-item Short Form Health Survey [SF-36], Dermatology Life Quality Index [DLQI]) as hypothesized. Correlations with the DLQI were moderate and ranged from 0.489 (symptom severity) to 0.521 (sign severity); those with SF-36 bodily pain were moderate to strong and ranged from -0.624 (sign severity) to -0.682 (symptom severity)[9].
- For assessment of divergent validity, the PSSD-24h was weakly correlated (<0.300) with several SF-36 scales as hypothesized, including SF-36 role physical, SF-36 vitality, SF-36 role emotional, SF-36 mental health and SF- 36 mental component summary scores.

Responsiveness (Ability to Detect Change)

- For assessment of responsiveness, moderate changes in scores were observed for patients who rated themselves as improved or worsening based on responder groups created from the Patient Global Impression (PGI) scale. Among those rating themselves as improved from week 1 to week 2 on the PGI, there was a decrease (improvement) in PSSD-24h severity scores. Small changes in scores were seen in those rating themselves as unchanged, while those rating themselves as worse on the PGI appropriately demonstrated increases in PSSD severity score indicating worsening.

  Reviewer's comment(s): *The changes in scores were presented by the standardized effect size (SES)[10], standardized response mean (SRM)[11] and Guyatt's statistics[12]. The data from these analyses should be interpreted cautiously as the changes seen in the PSSD-24h was numerically small for both improvement and worsening categories. Additionally, there were minimal patients who were categorized as improved (n= 5). Statistical significance was not evaluated.*

[8] Subjects were grouped according to baseline PASI score (<13, 13–16.9, ≥17), baseline PGI rating, and day-7 DLQI score (≤6, 7–15, ≥16). In each case, subjects in the most severe disease group produced the highest PSSD symptom and sign severity scores.
[9] The negative correlations to the SF-36 items are because lower scores on SF-36 indicates worse disease, whereas higher scores on the PSSD indicate worse disease.
[10] SES was calculated as the difference in means between Week 1 and Week 2 scores divided by the Week 1 standard deviation.
[11] SRM was calculated as the difference in means between Week 1 and Week 2 scores divided by the Week 1 standard deviation.
[12] Guyatt's statistics was calculated as the difference in means between Week 1 and Week 2 PSSD-24h scores divided by the standard deviation of the change score for stable patients. Stable patients were defined as those who rated themselves as unchanged on the PGI at Day 14.

Reviewer's comment(s):
Based on prior review of this instrument, the estimates for internal consistency reliability, test-retest reliability, convergent and divergent validity were within acceptable and reasonable ranges for the respective analysis. Known groups validity and responsiveness could not be adequately assessed due to small sample sizes within the categorized reference groups. This reviewer does not have significant concern regarding the reliability and validity of this instrument based on the cited literature (Feldman et al., 2016) and previous experience with the instrument in the guselkumab development program.

5.6 Interpretation of Meaningful Within-Patient Score Changes

The applicant performed a pre-specified analysis (secondary endpoint) evaluating the proportion of patients achieving a PSSD Symptom score of 0 (symptom absent).

Reviewer's comment(s):
The pre-specified secondary COA endpoint assesses clinical benefit via the targeted response of complete resolution of symptoms.

The applicant performed the following analyses to support the threshold(s) for meaningful within-patient score change in the PSSD Symptom domain score:

- Anchor-based analyses
  - Distribution of change on the target COAs by change on anchors
  - Anchor-based empirical cumulative distribution function and probability density function curves
- Distribution-based analyses

The applicant proposed the following thresholds for meaningful within-patient score change for the PSSD Symptom score (Table 3):

Table 4. Summary of PSSD meaningful change thresholds for improvement estimates

PSSD Score	Anchor-based Estimates	Distribution-based Estimates		MCT Recommendations		
		0.5 SD	SEM	Smallest meaningful change	Concordance between anchors	Hyper-responder threshold
Symptom score	14.8, 23.7	12.8	5.8	15	25	30

Anchor-based Analyses
Table 4 (shown on next page) summarizes the anchor scales used by the applicant in Studies IM011-046 and -047 and their corresponding target COA. This submission did not include copies of the anchor scales.

Table 4. Summary of Anchor Scales

Endpoint concept/attribute (COA type/name if any)	Anchor (concept)	Anchor response scale	Recall period (target/anchor)	Assessment schedule (target/anchor)
PSSD Symptom domain score (symptom severity)	PGI-S (symptom severity)	4-point VRS: None, Mild, Moderate, Severe	Previous 24 hours/ Momentary ("Currently")	Daily/ Baseline, Weeks 16, 24, and 52
	PGI-C (change in disease status)	7-point VRS: Very much worse, Moderately worse, A little worse, No change, A little better, Moderately better, Very much better	Previous 24 hours/ comparison of current state to earlier period ("Since you started taking the study medication")	Daily/ Baseline, Weeks 16, 24, and 52

PGI-S= Patient Global Impression of Severity; PGI-C= Patient Global Impression of Change

Reviewer's comment(s): *It should be noted that while the anchor correlation coefficients[13] with the PSSD Symptom domain score at baseline were deemed acceptable by the applicant, this reviewer notes the following limitations regarding the PGI-C anchor scale:*

- *The concept measured in the PGI-C scale ("overall change in psoriasis") is not aligned with the concept measured in the PSSD Symptom domain score ("psoriasis symptom severity"). An anchor scale measuring the same concept (i.e., the aspect of the disease specified in the endpoint, as opposed to global status of the disease) provides the most direct evidence.*
- *Potential susceptibility to recall error due to its recall period (i.e., participant has to recall over 16 weeks).*

However, this reviewer acknowledges that the PGI-C may still be informative.

For the PSSD Symptom domain scores at Week 16, the "a little better" category on the PGI-C attained a significant within-group improvement ($p < 0.0001$) with a moderate SES (0.73). The 95% confidence intervals (CIs) for the "a little better" category (-22.8, -14.71) and the "no change" category (-10.9, -0.56) did not overlap. A score decrease of at least 14.8 was identified as the lowest level of change that fell outside the no change CI but within the significant change category.

For the PGI-S anchor, the 1-point improvement category attained a significant within-group improvement ($P < 0.0001$) with a large SES (1.03). The 95% CIs for the 1-point improvement category (-29.3, -23.62) and the "no change" category (-8.2, -2.15) did not overlap. A score decrease of at least 23.7 was identified as the lowest level of change that fell outside the no change CI but within the significant change category.

[13] The correlation coefficients ranged from 0.361 to 0.413; and the correlation coefficients for change from baseline to Week 16 were > 0.50. A correlation coefficient of ≥ 0.40 was considered high per Applicant.

Reviewer's comment(s): *This reviewer does not agree with the applicant's approach to derive the meaningful change threshold for each PSSD score as it is based on distribution-based methods which we view as supportive to anchor-based methods. Additionally, it only identifies the lowest improvement category on the anchor with an SES ≥ 0.5 and a significant p-value. From a regulatory standpoint, we are more interested in what constitutes a clinically meaningful within-patient change in scores (i.e., improvement threshold), from the patient perspective, rather than a minimal improvement. It is unknown whether a 1-point improvement category in the PGI-S anchor or the "A little better category" in the PGI-C anchor constitutes a meaningful change for the respective anchor scale in the absence of patient input.*

Distribution-based Analyses
Distribution-based meaningful change threshold estimates are summarized in Table 5.

Table 5. Distribution-based Thresholds for the PSSD Symptom domain at Baseline

PSSD Score	N	0.5 SD	Cronbach's Alpha	SEM[a]
Symptom score	601	12.796	0.948	5.808

Reviewer's comment(s): *The applicant acknowledges that distribution-based thresholds are only supportive to the anchor-based estimates.*

6. APPENDICES

Appendix A: Psoriasis Symptom and Sign Diary

Appendix A: Psoriasis Symptom and Sign Diary

PSORIASIS SYMPTOMS AND SIGNS DIARY (PSSD)

Please answer each question to the best of your ability. There are no right or wrong answers. Please pay close attention to the time period of interest. These questions ask you to think about the **past 24 hours. Please complete the diary at the same time every day.**

Individuals with psoriasis may experience a range of symptoms. Please indicate how severe each of the following skin symptoms was in the **past 24 hours**. Please select only one number for each item on the 0 to 10 scale (0=Absent and 10= Worst imaginable).

1. Rate the severity of itch in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
2. Rate the severity of dryness in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
3. Rate the severity of cracking in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
4. Rate the severity of skin tightness in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
5. Rate the severity of scaling (build-up of skin) in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
6. Rate the severity of shedding or flaking in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
7. Rate the severity of redness in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
8. Rate the severity of bleeding in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
9. Rate the severity of burning in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
10. Rate the severity of stinging in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
11. Rate the severity of pain from your psoriasis lesions in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable

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/s/

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DAVID S REASNER
08/26/2022 07:30:37 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	August 9, 2022
To:	Jennifer Harmon, PharmD Regulatory Project Manager **Division of Dermatology and Dentistry (DDD)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Laurie Buonaccorsi, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	James Dvorsky, PharmD Team Leader **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	SOTYKTU (deucravacitinib)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 214958
Applicant:	Bristol-Myers Squibb Company

1 INTRODUCTION

On September 10, 2021, Bristol-Myers Squibb Company submitted for the Agency's review an original New Drug Application (NDA) 214958 under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for SOTYKTU (deucravacitinib) tablets. The proposed indication for SOTYKTU (deucravacitinib) tablets is for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dentistry (DDD) on October 4, 2021, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for SOTYKTU (deucravacitinib) tablets.

2 MATERIAL REVIEWED

- Draft SOTYKTU (deucravacitinib) tablets MG received on April 29, 2022, and received by DMPP and OPDP on August 5, 2022.
- Draft SOTYKTU (deucravacitinib) tablets Prescribing Information (PI) received on September 10, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 5, 2022.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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LASHAWN M GRIFFITHS
08/09/2022 04:11:09 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 8/8/22

To: Jennifer Harmon, Regulatory Project Manager, (DDD)

From: James Dvorsky, Team Lead
Office of Prescription Drug Promotion (OPDP)

CC: Carrie Newcomer, Regulatory Review Officer, OPDP

Subject: OPDP Labeling Comments for SOTYKTU (deucravacitinib)

NDA/BLA: NDA 214958

In response to DDD's consult request dated October 4, 2021, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling, for the original NDA submission for Sotyktu.

Labeling: OPDP's comments on the proposed PI are based on the draft labeling received by electronic mail from DDD on August 5, 2022 and are provided below.

OPDP comments on the proposed Sotyktu PPI will be sent under separate cover, as a combined OPDP and Division of Medical Policy Programs (DMPP) review.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on June 1, 2022, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact James Dvorsky at james.dvorsky@fda.hhs.gov.

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JAMES S DVORSKY
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Clinical Inspection Summary

Date	03 Aug 2022
From	Elena Boley, M.D., M.B.A. Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Jennifer Harmon, PharmD., RPM Maryjoy Mejia, M.D., Medical Reviewer Amy Woitach, D.O., Medical Team Leader Kendall Marcus, M.D., Division Director Dermatology and Dentistry
NDA #	214958
Applicant	Bristol-Myers Squibb Company
Drug	Deucravacitinib, BMS-986165
NME	Yes
Proposed Indication	Treatment of moderate to severe plaque psoriasis
Consultation Request Date	16 Nov 2021
Summary Goal Date	10 Aug 2022
Action Goal Date	24 Aug 2022
PDUFA Date	10 Sep 2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Naranjo Lopez, Sofen, and Szepietowski as well as the sponsor, Bristol-Myers Squibb (BMS), were inspected in support of NDA 214958. These inspections covered Protocols IM011046 and IM011047. Despite some protocol deviations that are discussed in the Results section (section III, subheading 4), the studies overall appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

II. BACKGROUND

NDA 214958 was submitted in support of the use of deucravacitinib (BMS-986165) [DEUC] tablet 6 mg for the treatment of adults with moderate-to-severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy. The two pivotal studies supporting the application were the following:

- Protocol IM011046: A Multi-Center, Randomized, Double-Blind, Placebo- and Active Comparator-Controlled Phase 3 Study to Evaluate the Efficacy and Safety of BMS-986165 in Subjects with Moderate-to-Severe Plaque Psoriasis

- Protocol IM011047: An Investigational Study to Evaluate Experimental Medication

BMS-986165 Compared to Placebo and a Currently Available Treatment in Participants With Moderate-to-Severe Plaque Psoriasis

These two studies were similarly designed (identical up to Week 24) 52-week, randomized, double-blind, placebo- and active comparator-controlled, multicenter studies in subjects with moderate to severe plaque psoriasis. Study IM011047 additionally has a randomized withdrawal and maintenance period.

Eligible subjects were adult males and females who had moderate-to-severe plaque psoriasis (defined as Psorasis Area and Severity Index [PASI] score ≥ 3, and Body Surface Area [BSA] involvement ≥10% at both Screening Visit and Day 1). Subjects were required to have stable plaque psoriasis (defined as no morphology changes or significant flares of plaque psoriasis in the opinion of the investigator) for at least 6 months. To be eligible, subjects also had to be deemed candidates for phototherapy or systemic therapy by the investigator.

The protocols for both pivotal studies specified the following ***co-primary efficacy endpoints***:

- Proportion of subjects achieving the psoriasis Physician's Global Assessment (sPGA) score of 0 (clear) or 1 (almost clear) with at least a 2-grade of improvement from baseline to Week 16.
- Proportion of subjects with ≥75% improvement in the Psorasis Area and Severity Index (PASI-75) from baseline to Week 16.

The Physician's Global Assessment (sPGA) is a 5-point scale of an average assessment of all psoriasis lesions based on the following three scales: erythema, scaling, and induration. The sPGA measure was used to determine psoriasis severity at a single point in time (without taking into account the baseline disease condition) as clear (0), almost clear (1), mild (2), moderate (3), or severe (4). The final sPGA score is the average of the three scales, rounded to the nearest whole number. A decrease in sPGA score over time reflects improvement. An sPGA 0/1 response is defined as an sPGA score of 0 or 1 in subjects with ≥2-point improvement from baseline.

The PASI is a measure of the average redness, thickness, and scaliness of psoriasis skin lesions (each graded on a 0-4 scale), weighted by the area of involvement (head, arms, trunk to groin, and legs to top of buttocks). The PASI produces a numeric score that can range from 0 to 72, with higher PASI scores denoting more severe disease activity. PASI-75 is the proportion of subjects who experienced a ≥75% improvement from baseline in the PASI score. (b) (4) (b) (4) was used for the data collection and the management of electronic clinical outcome assessments (eCOA) and provided a tablet for the clinical investigator to record the sPGA score and PASI data during clinic visits.

Details relevant to Study IM011046

Study IM011046 was conducted at 154 centers that randomized subjects in 11 countries (Canada, China, Germany, Japan, Poland, Russia, South Korea, Spain, Taiwan, United Kingdom, and the United States). The first subject was screened on August 7, 2018, and the last subject completed their final visit on September 2, 2020. Of the 666 subjects that were enrolled, 535 completed the study. The original protocol was dated May 18, 2018, with 5

protocol amendments. The final protocol amendment was dated December 17, 2019.

The study consisted of three periods: screening (up to 4 weeks), treatment (52 weeks), and follow-up (4 weeks).

After the screening period, eligible subjects were randomized in a blinded fashion in a (2:2:1) ratio to receive DEUC 6 mg daily, placebo daily, or apremilast titrated to 30 mg twice daily, respectively. Randomization was stratified by geographic region (US, Japan, China, and rest of world), previous biologic use (for psoriasis, psoriatic arthritis, or other inflammatory diseases only; yes/no), and body weight (≥90 kg and <90 kg; body weight stratum not applied in Japan or China).

At Week 16, the co-primary endpoints (sPGA 0/1 and PASI-75) were assessed. All subjects who received placebo were switched in a blinded manner to DEUC 6 mg QD, while subjects who were randomized to DEUC 6 mg QD or apremilast 30 mg BID continued the same treatment regimen through Week 24.

At Week 24, subjects continued their treatments except those subjects on apremilast who did not achieve a PASI score equal to 50% improvement (PASI-50) response were switched to DEUC 6 mg QD.

At Week 52, the treatment period ended, and subjects could continue on to participate in long-term extension (LTE) Study IM011075 or complete the final safety follow-up visit 4 weeks later.

Details relevant to Study IM011047

Study IM011047 was conducted at 191 centers that randomized subjects in 16 countries (Australia, Canada, Czech Republic, Finland, France, Germany, Hungary, Israel, Italy, New Zealand, Poland, Puerto Rico, Spain, Sweden, UK, and USA). The first subject was screened on July 26, 2018, and the last subject completed their final visit on November 30, 2020. Of the 1019 subjects that were enrolled, 751 subjects completed the study. The original protocol was dated May 11, 2018, there was one protocol amendment, and the final protocol was dated June 15, 2018.

The study consisted of three periods: screening (up to 4 weeks), treatment (24 weeks), re-randomization and withdrawal (28 weeks), and follow-up (4 weeks).

After the screening period, eligible subjects were randomized in a blinded fashion in a (2:2:1) ratio to receive DEUC 6 mg daily, placebo daily, or apremilast titrated to 30 mg twice daily, respectively. Randomization was stratified by geographic region (US and rest of world), previous biologic use (for psoriasis, psoriatic arthritis or other inflammatory diseases only; yes/no), and body weight (≥ 90 kg and <90 kg).

At Week 16, the co-primary endpoints (sPGA 0/1 and PASI-75) were assessed. All subjects who received placebo were switched in a blinded manner to DEUC 6 mg QD, while subjects

who were randomized to DEUC 6 mg QD or apremilast 30 mg BID continued the same treatment regimen through Week 24.

At Week 24, based on their PASI response, subjects either continued their treatments or were switched to DEUC or placebo, and continued their treatment through Week 52.

At Week 52, the treatment period ended, and subjects could continue on to participate in long-term extension (LTE) Study IM011075 or complete the final safety follow-up visit 4 weeks later.

Rationale for Site Selection

The two domestic clinical sites (Drs. Naranjo Lopez and Sofen) were chosen primarily based on numbers of enrolled subjects, site-specific efficacy results, and lower than average protocol deviations. The sponsor was chosen for inspection because this was an NME and due to a reported IRT error (see sponsor section below for more details). The foreign clinical investigator site (Dr. Szepietowski in Poland) was selected for inspection because of insufficient domestic data for Study IM011046. For this study, 33% of total subjects were enrolled in the US (38% of sites). The Eastern Europe region enrolled the largest number of subjects.

III. RESULTS (by site):

1. **Hector Naranjo Lopez, M.D.**
   Site #62
   16420 Northwest 59th Avenue
   Miami Lakes, FL 33014
   *PDUFA Inspection Dates:*18-27 Jan 2022

At this site for Protocol IM011046, 28 subjects were screened, 19 were randomized, and 14 subjects completed the study. Of the 5 subjects who terminated early, 4 withdrew consent and 1 was terminated at the request of the physician (enrollment log shows “early termination” but line listings show subject withdrew from the study due to reasons related to her job per line listings).

The inspection evaluated the study records for the 19 randomized subjects. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; institutional review board (IRB) submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records and other regulatory documentation (e.g., Form FDA 1572s); primary efficacy endpoint data; adverse event reporting; protocol deviations; drug accountability logs; and monitor logs and follow-up letters.

There was no evidence of under-reporting of adverse events. Certified copies of the primary efficacy endpoint data were sent by (b) (4) to the clinical investigator (CI) via a CD-ROM. The sPGA scores and the PASI-75 scores at both Week 0 and Week 16 were verified against the

data line listings provided by the sponsor for all 19 randomized subjects. No discrepancies were noted.

2. **Howard Sofen, M.D.**
   Site #160
   8930 S Sepulveda Blvd Ste 114
   Los Angeles, CA 90045-3606
   *PDUFA Inspection Dates:*14 March 2022 to 18 March 2022

At this site for Protocol IM011047, 30 subjects were screened, 25 were randomized, one was withdrawn from the study (moved abroad), and 24 subjects completed the study.

The inspection evaluated the informed consent, co-primary endpoints, and adverse events for all 25 randomized subjects. In addition, an audit was conducted for 15 of the 25 subjects for which the following records were reviewed: inclusion/exclusion criteria and study visit information; the study protocol and amendments; institutional review board (IRB) submissions, approvals, and correspondence; source records, including medical records and other regulatory documentation (e.g., Form FDA 1572s); primary efficacy endpoint data; adverse event reporting; protocol deviations; drug accountability logs; and monitor logs and follow-up letters.

There was no evidence of under-reporting of adverse events. PDF extractions of the primary efficacy endpoint data were sent by (b) (4) to the CI. During the inspection, the PDF data were reviewed, and the sPGA scores and the PASI-75 scores at both Week 0 and Week 16 were verified against the data line listings provided by the sponsor for all 25 randomized subjects. No discrepancies were noted.

3. **Jacek C. Szepietowski, M.D.**
   Site #105
   Ul. Sliczna 13, Lukasz Matusiak 4health,
   Wroclaw, PL
   PDUFA Inspection Dates: 07 March 2022 to 10 March 2022

At this site for Protocol IM011046, 30 subjects were screened, 22 were randomized, and all randomized subjects completed the study. According to the ADaM Subject-Level data files submitted with complete study report, 29 subjects were screened (one subject was screened twice and counted twice in the on-site screening log), 5 failed screening (one subject was counted twice in the on-site screening log), and 2 discontinued after they withdrew consent (in on-site log, these subjects withdrew consent prior to randomization).

The inspection evaluated the study records for the 22 randomized subjects. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; institutional review board (IRB) submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records and other regulatory documentation (e.g., Form FDA 1572s); primary efficacy endpoint data; adverse event reporting; protocol deviations; drug accountability logs; and monitor logs and follow-up letters.

Adverse events and primary efficacy records were reviewed for 8 of the 22 randomized subjects. There was no evidence of under-reporting of adverse events. After study closure, the sponsor provided the site with copies of the final versions of the source efficacy data (presumably from (b) (4), though not specified in the establishment inspection report). During the inspection, the sPGA scores and the PASI-75 scores at both Week 0 and Week 16 were verified against the data line listings provided by the sponsor. No discrepancies were noted.

4. Bristol-Myers Squibb
Route 206 & Province Line Road,
Princeton, NJ, 08543-4000, US
PDUFA Inspection Dates: 21 January 2022 to 02 February 2022

This inspection covered the sponsor practices related to Protocols IM011046 and IM011047 and focused on the three clinical investigator sites (sites #62 and #105 from Study IM011046], and #160 from Study IM011047) that had been selected for inspection.

Records reviewed included, but were not limited to, vendor, site investigator, and site monitoring; Standard Operating Procedures (SOP); training records; clinicaltrials.gov; Form FDA 1572; financial disclosure; quality assurance activities, including audit plans; handling of safety reports; monitoring boards; data collection; protocol deviations; and investigational product handling.

Clinical monitoring for these protocols was performed by (b) (4) (b) (4). The monitors appeared to have the required minimum experience and training prior to the study, and monitors appear to have conducted adequate source data verification and source document review. Overall, no issues were found with the clinical monitoring of these two protocols.

The inspection reviewed protocol deviations in general and specifically for the three sites selected for inspection (sites #62 and #105 from Study IM011046 and site #160 from Study IM011047). One clinical site, site #92 from study IM011046, was terminated due to noncompliance with the protocols. Once BMS identified that site, a for-cause audit was performed by (b) (4), and the site was terminated prior to completion of the trial. This GCP non-compliance for site #92 appears to have been handled appropriately.

It was noted that there was a failure of the Interactive Response Technology (IRT) system to manage treatment assignment in Study IM011047 that resulted in 106 subjects not being switched to the DEUC arm as they should have been after they experienced a protocol-defined relapse during the randomized withdrawal period (Week 24). BMS considered “the event to be of Major Impact because it was a substantial deviation from the study design related to the IRT system for managing study treatment.” However, BMS maintained that the “issue did not have a significant impact on subject safety or on overall trial integrity.”

(b) (4) was responsible for the IRT for this study. Their root cause analysis determined that when system updates were made, inadequate detail was included in the Work Instruction User

Acceptance Testing (UAT) of eCLinical Data Systems (the IRT system) such that the change request UAT did not test whether integration of positive relapse responses into the IRT system resulted in a change of treatment dispensation. As a corrective action, (b) (4) updated the Work Instruction UAT to note that when system updates that impact critical workflows, including integration, are made, these scenarios should be considered, even if they were tested in prior UATs.

BMS claimed that the root cause was not with (b) (4) and not with BMS. Notwithstanding, BMS did establish a Preventative Action to revise BMS's Partnership Guidance with (b) (4) to include review and approval of UAT plans, test scripts, and the final report.

Reviewer's comment: This IRT error, affecting 106 subjects in Study IM011047, would not have an effect on the primary efficacy analysis, because it occurred on Week 24, 8 weeks after the primary endpoint was measured (Week 16) and during the randomized withdrawal and maintenance period (Weeks 24-52). However, this would impact subject safety, as these subjects who relapsed were not switched to the proper treatment as per the protocol. The corrective and preventative actions by (b) (4) and BMS appear to be adequate.

In terms of pharmacovigilance, the inspection found no deficiencies in the receipt, evaluation, and reporting of serious adverse events from CIs. BMS ultimately completed the final medical review and causality assessments to determine whether an expedited safety report was warranted.

The inspection also reviewed data collection and handling for both studies, including a review of the Clinical Management Plans and the collection of the primary efficacy endpoint data by the use of tablets provided by (b) (4) and though the (b) (4) database. Any technical issues where clinical sites could not access the device or outages (b) (4) were documented and followed-up by the clinical research associates and the (b) (4) managers. Weekly meetings with (b) (4) BMS, and (b) (4) were conducted.

{See appended electronic signature page}

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JENN W SELLERS
08/04/2022 09:33:39 AM

Division of Hepatology and Nutrition Consultation

Drug-induced Liver Injury Team

NDA	214958
Consultation Issue	Drug-induced liver injury (DILI)
Drug Product	Deucravacitinib (DEUC)
Indication	Plaque psoriasis (PsO)
Applicant	Bristol Myers Squibb
Requesting Division	Division of Dermatology and Dentistry (DDD)
Primary Reviewer	Ling Lan, MD, PhD Clinical Analyst, OND/DHN
Secondary Reviewer	Paul H. Hayashi, MD, MPH DILI Team Lead, OND/DHN
Reviewer **Office of Pharmacoepidemiology**	Mark Avigan, MD, CM Associate Director, OPE/OSE
Signatory Authority	Joseph Toerner, MD, MPH Director, OND/DHN
Assessment Date	July 29, 2022

Context: Deucravacitinib (DEUC) is a new molecular entity and small molecule that inhibits tyrosine kinase 2 (TYK2). The applicant claims DEUC is more selective than other Janus kinase inhibitors (JAKi). This NDA is for the treatment of plaque psoriasis (PSO). The Division of Dermatology and Dentistry (DDD) noted one potential Hy's law case and several subjects exposed to DEUC with elevations in liver biochemistries. They requested the DILI Team's assessment of the applicant's hepatic safety analyses and advice on labeling.

Executive Summary: We do not see a drug-induced liver injury (DILI) risk that would prevent approval of DEUC. The potential Hy's Law case found by DDD had a non-DILI etiology, so there were no Hy's Law cases in the integrated safety summary population. The differences in liver enzyme elevations between DEUC exposed subjects, active comparator (apremilast) and placebo were mixed without a clear concern for liver injury risk with DEUC, particularly at ALT levels over 5x ULN. Case level analyses did not reveal any probable DILI cases attributable to DEUC. There was one subject who died of rapidly progressive cancer raising the possibility of DUEC's role in accelerating the tumor growth and spread. Mention of this case and possible risk of cancer in the label similar to other JAKis may be considered. Though subjects with positive hepatitis B serologies were excluded from the clinical trials, mention of hepatitis B reactivation risk similar to other JAKis should be considered.

Full Consultation Sections:

Section 1.0 – Disease and Rationale
Section 2.0 - ADME pertinent to DILI

Section 3.0 - Non-clinical data pertinent to DILI.
Section 4.0 - Clinical data
Section 5.0 – Assessment & Recommendations.

Abbreviations:
ALP: alkaline phosphatase
ALT: alanine aminotransferase
AP: alkaline phosphatase
AST: aspartate aminotransferase
BMS-986165: deucravacitinib or DEUC
BSA: body surface area
DB: direct bilirubin
DDI: drug-drug interaction
DEUC: deucravacitinib or BMS-986165
DILI: drug-induced liver injury
DMC: Data Monitoring Committee
GGT: gamma-glutamyl transferase
HCC: hepatocellular carcinoma
IL: interleukin
ISS: integrated safety summary
JAKi: Janus kinase inhibitor
PASI: psoriasis area and severity index
PI: package insert
PsA: psoriatic arthritis
PsO: plaque psoriasis
RA: rheumatoid arthritis
sPGA: static physicians' global assessment
STAT: signal transducer and activator of transcription
TB: total bilirubin
TNF: tumor necrosis factor
TYK2: tyrosine kinase 2

1.0 Disease and Rationale:

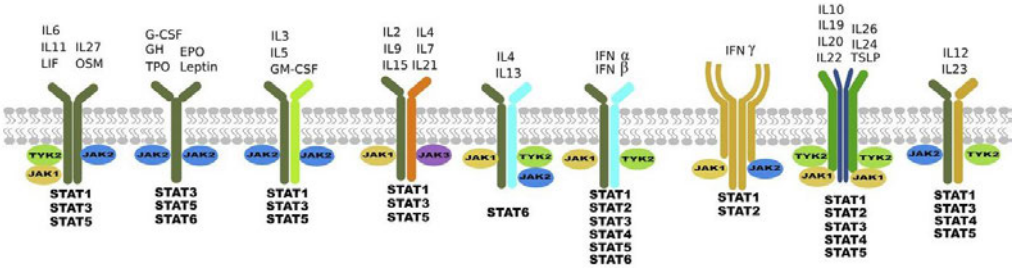
1.1 Disease: Psoriasis is a systemic disease, but its predominant clinical presentation and symptoms are dermatologic changes including erythematous plaques of hyperplastic skin cells. It a common disorder effecting all ages and across different races. However, it is less common before adolescence and less common to rare in certain races (e.g. Japanese, Alaska natives, West African blacks)[1]. Estimates of prevalence range from 0.5 to 11.4% in adults and up to 1.4% in children[2]. The four major types are chronic plaque, guttate, pustular and erythrodermic[3]. Plaque type is the most

[1] Farber EM et al. Dematologica (1974)
[2] Michalek IM, et al. JEur Acad Dermatol Venereol (2017)
[3] UpToDate. www.uptodate.com (accessed July 18, 2022)

common at around 75%. Non-skin manifestations include arthritis (30% of cases) and eye manifestations (e.g., uveitis). Skin manifestations lead to significant morbidity, including social inhibition and depression.

Pathophysiology is based on a complex interplay of T-lymphocytes, dendritic cells and cytokines, including interleukin-23 (IL-23), IL-17 and tumor necrosis factor (TNF). These cytokines act via the JAK/STAT pathway to induce inflammation and alter the immune responses in psoriatic diseases. Figure 1 below shows cytokines and hormones that utilize a variety of JAK combinations[4].

Figure 1: Cytokines and hormones that engage JAK-STAT.

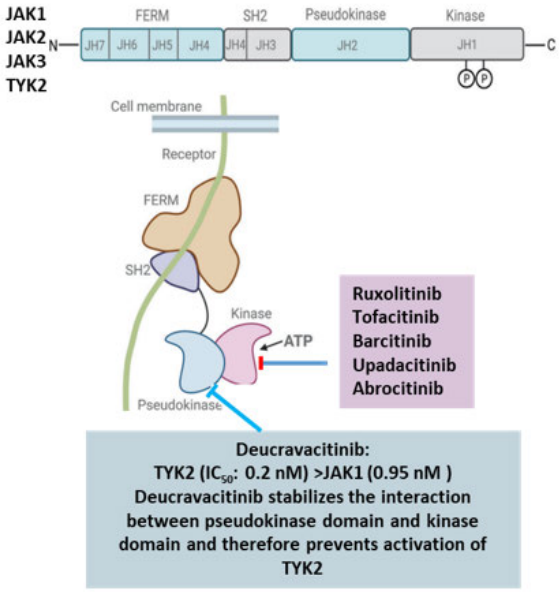


1.2 Rationale (mechanism of action): Current therapy options are many and range from topicals and phototherapy to oral immunosuppressive and immunomodulatory agents to injected monoclonal antibodies targeting TNF-alpha, IL-12/23 and IL-17A.

DEUC is an oral, selective TYK2 inhibitor. TYK2 is required for signal transduction and cellular functions downstream of interferons (IFN), IL-23, and IL-12 which are involved in the initiation and pathogenesis of psoriatic diseases. According to the Applicant, DEUC achieves selective TYK2 inhibition by binding to the pseudokinase domain of TYK2 and locking the kinase in an inactive state (Figure 2). This binding site for DEUC in the pseudokinase domain is separate and distinct from the kinase domain binding site for currently marketed, ATP-competitive JAK inhibitors.

Figure 2: Deucravacitinib binding in JAK-STAT pathway

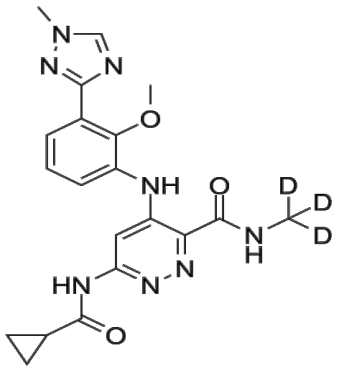
[4] https://pharmrev.aspetjournals.org/content/72/2/486 Pharmacol Rev 72:486-526



2.0 ADME data pertinent to DILI:

2.1 Chemical structure of deucravacitinib (BMS-986165)

Figure 3: Skeletal formula of deucravacitinib



2.2 Absorption: [^{14}C] BMS-986165-derived radioactivity was quickly absorbed and distributed to tissues following a single PO dose of 20mg/kg to male rats. Following oral administration of a solution at 10mg/kg in mice, BMS-986165 was rapidly absorbed with T_{max} of 0.5 hour and fraction absorption (F) = 100%. Similar results were obtained with oral administration of a suspension at the same dose, but F was 73% in this case. In rats following an oral administration of 10mg/kg of a solution, T_{max} was 1.67hrs and F>100%. A suspension at the same dose was also rapidly absorbed with a T_{max} of 1 hour and F of 67%. In dogs, after an oral administration of 10mg/kg, BMS 986165 was rapidly absorbed and T_{max} came out to be 2 hours and F>100%. Studies done in monkeys showed a slow absorption following an oral administration of BMS-986165 with T_{max} of 5 hours and F > 87%. There was an extravascular distribution in the above studies. Pyrimethamine is inhibitor of OCT and inhibited the uptake of BMS-986165 suggesting that OCT

transporters play a role in the hepatic uptake of BMS-986165. Overall, oral absorption of DEUC is expected to be quick and robust.

2.3 Distribution: A study based on eleven male rats showed that [^{14}C]BMS-986165 at the PO dose of 20mg/kg was widely distributed with the highest concentrations found in bile, liver, and adrenal glands. During the time dependent measurement following a bidirectional permeability assay, the transport of BMS-986165 was linear for 2 hours for both BCRP and MDR1 transporters indicating no significant inhibition. BMS-986165 did show inhibition of BSEP (71%) and MRP2 (26%) at maximal concentrations. (Table 1)[5]

Table 1

Inhibition of Human Hepatobiliary and Renal Transporters Assay Results

Transporter	Probe Substrate	IC50 (μM)	% Inhibition at Max Concentration
OATP1B1	Pitavastatin	6.1 ± 1.0	90 ± 8
OATP1B3	Cholecystokinin-Octapeptide	1.1 ± 0.4	99 ± 2
NTCP	Sodium Taurocholate	> 50	-16 ± 20
BSEP	Sodium Taurocholate	17.0 ± 2.1	71 ± 2
MRP2	Estradiol-17-β-Glucuronide	> 50	26 ± 14
OAT1	Para-aminohippurate	16.8 ± 2.7	82 ± 8
OAT3	Estrone-3-sulfate	17.2 ± 0.9	74 ± 6

Values are mean ± standard deviation, N = 3, except OAT1 (N = 2) and BSEP (N = 4).
Max Concentration = the highest tested concentration of BMS-986165 that is not affected by compound precipitation in the assay buffer (50 μM).
Targeted test concentrations of BMS-986165 were: 50, 16.6, 5.55, 1.85, 0.62, 0.206, 0.069, 0.023, 0.0076, and 0.0025 μM.
Negative % Inhibition values may reflect assay interference or potential transporter activation effects, or variability around zero-baseline.
Results Electronic Notebook references: A022B-025, A022B-026, A022B-029, A022B-030.
Summary Electronic Notebook reference: 91675-041.

BMT-158170 which is a metabolite of BMS-986165, at the maximum concentration showed inhibitions of 75% and 81% respectively for BSEP and MRP2. (Table 2)

Table 2:

[5] docubridge://open/Server=CDER-PRODUCTION&Id=Fa4045dcb06da4c64a40cb0d0badfdd28&NodeId=N3382b17ea1bc4801ab647641c620e514&Page=86

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Inhibition of Human Hepatobiliary and Renal Transporters Assay Results

Transporter	Probe Substrate	N	IC50 (μM)	% Inhibition at Max Concentration
	...statin	4	> 50	17 ± 10
OATP1B3	Cholecystokinin-Octapeptide	4	> 50	35 ± 3
NTCP	Sodium Taurocholate	5	> 50	-2 ± 9
BSEP	Sodium Taurocholate	6	> 50	20 ± 8
MRP2	Estradiol-17-β-Glucuronide	6	> 50	25 ± 15
OAT1	Para-aminohippurate	6	> 50	25 ± 5
OAT3	Estrone-3-sulfate	3	15.8 ± 1.8	85 ± 14
OCT1	Metformin	6	19.9 ± 2.4	74 ± 7
OCT2	Metformin	6	> 50	16 ± 17
MATE1	Metformin	5	16.0 ± 1.6	54 ± 2

Values are mean ± standard deviation.
N = number of individual values used to calculate the mean and standard deviation in a given assay.
Max Concentration = the highest tested concentration of BMT-158170 that is not affected by compound precipitation in the assay buffer (50 μM).
Six (6) separate samples of BMT-158170 were tested in a single experiment in duplicate. Data points from the duplicates were fitted together to generate a single IC50 and % Inhibition result value, thus, resulting in a total of 6 values (N = 6). If the data from any of these 6 test instances did not satisfy assay QC criteria, the corresponding results were not reported, thus, resulting in N < 6.
Targeted test concentrations of BMT-158170 were: 50, 16.6, 5.55, 1.85, 0.62, 0.206, 0.069, 0.023, 0.0076, and 0.0025 μM.
Negative % Inhibition values may reflect assay interference or potential transporter activation effects, or variability around zero-baseline.
Results Electronic Notebook references: A0F54-091, A0F54-092, A0F54-093, A0F54-097, A0F54-098.
Summary Electronic Notebook reference: 86576-057.

6

The formula for percent inhibition calculation is below:

Results were expressed as percent inhibition, calculated as:

$$\%\ Inhibition = \left(1 - \frac{S - B}{T - B}\right) \times 100$$

Where:

T = average maximal control,

B = average background,

S = sample signals.

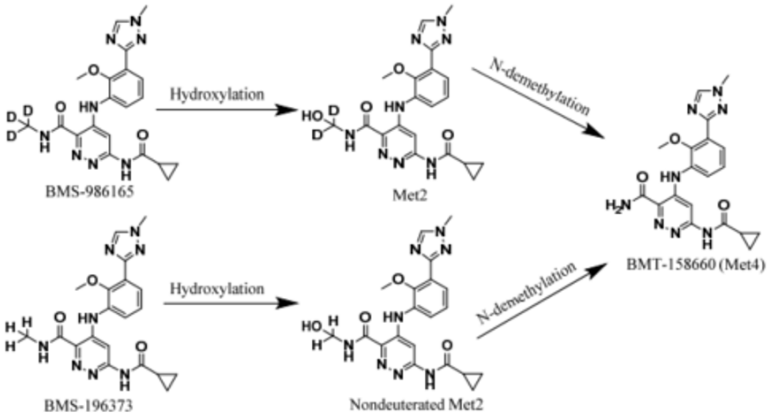
The results were then imported into custom curve fitting software, which utilizes (b) (4) (b) (4) to determine the IC50 values for each test compound.

BMT-153261 is a substrate of MATE2-K but not for OAT1, OAT1, OAT3, OCT2, MATE1. BMS-986165 is not substrate of human OAT1, OAT1, OAT3, OCT2, MATE1, or MATE2-K.

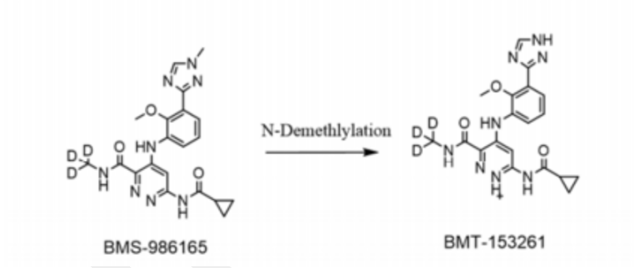
2.4 Metabolism: The major in vivo biotransformation pathways in rats if [^{14}C] BMS-986165 are cyclopropyl carboxamide hydrolysis, N-demethylation, mono-oxidation, direct glucuronidation of the parent drug, demethylation of the deuterated methyl group. (Figure 4) Unchanged parent drug is the most prominent circulating component (75% of the plasma radioactivity) in plasma from intact rats. CYP1A2, CYP2B6, CYP2D6, and CYP3A4 were the major enzymes involved in the formation of BMT-153261, and CYP2b6 and CYP2d6 the major enzymes involve in the formation of Met2. The turnover of BMS-986165 was low in a reaction phenotyping study with recombinant human cytochrome P450 enzymes. Thus, the predominant circulating form of BMS-986165 would be expected to be parent compound in humans.

Figure 4: Postulated metabolites for BMS-986165 (DEUC)

[6] docubridge://open/Server=CDER-PRODUCTION&Id=Fa4045dcb06da4c64a40cb0d0badfdd28&NodeId=N9199d11f6b5e4d60a98ce7c4aa491cda&Page=89



The Major Metabolic Pathway of BMS-986165 in Human Liver Microsomes



BMS-986165 does not induce CYP1a2, CYP2B6, or CYO3A4 in human hepatocyte as compared to control. In a three-month study in rats, the NOAEL was 15mg/kg/day and the mean AUC [0-24h]: 17.6 µg.h/mL.

2.5 Excretion: [^{14}C] BMS-986165-derived radioactivity following a single PO dose of 20mg/kg to male rats was rapidly eliminated. Most tissues were below the quantifiable limit at 48 hours post dose. Renal and fecal excretion played an important role in the elimination of BMS-986165 which is the major drug related component in urine and feces with 12.9% and 25.9% of the total radioactivity respectively. 59.3% of the dose was eliminated as metabolites suggesting that metabolism is the major route of elimination for BMS-986165. The predominant route of elimination of radioactivity was biliary from male monkeys following an oral dose of [^{14}C]BMS-986165. Biliary excretion accounted for a mean recovery of 59.8%, fecal excretion (15.6%), and urine excretion (14.4%). The oral dose was well absorbed since the mean amount of radioactivity eliminated in bile and urine was 74%. In male hybrid mice the data showed that feces was the main route of excretion [^{14}C] BMS-986165-derived radioactivity. In rats, metabolic clearance was the major route of elimination. Thus, feces (via bile) is the major route of elimination of metabolites but there is a modest amount excreted in urine as well.

3.0 Non-clinical data related to DILI and carcinoma risk:

3.1 In vitro studies: In cynomolgus monkeys' whole blood, BMS-986165 inhibited IFNα-induced phosphorylation of STAT1 and STAT5 in CD3+ T cells with an IC50 value of 17 and 20 nM, respectively. STAT1 is a tumor suppressor. Loss of STAT1 protein expression has been observed in cancer (Thomas et al, 2004)[7]. STAT1 may also function as a regulator of hepatocellular carcinoma (HCC) cell apoptosis and cell cycle arrest (Chen et al, 2015)[8]. Type 1 interferon-inducible transcript were decreased in monkeys' blood cells following a single PO dose of 3, 10, or 30mg/kg/day of BMS-986165, this was consistent with the expected pharmacologic activity of TYK2 inhibition. We found no Interleukin-15 assays that might inform carcinogenicity of this drug, but inhibition of STAT1 is known to effect IL-15 levels.

3.2 Animal studies:

3.2.1 Liver injury marker data**:** No glutathione conjugates were detected. There was a dose related and statistically significant repression of type IFN-inducible genes following a 3 month of once daily oral dosages of 2, 5, or 15 mg/kg/day of BMS-986165 to rats. It was reported that the expected pharmacologic response to Tyk2 inhibition was noted in liver. A significant increase in bilirubin was observed in this three-month study in rats but was mainly related to a transient BMS-986165-mediated inhibition of UDP glucuronosyltransferase 1A1 enzyme activity. This was not considered as adverse, due to the lack of any other clinical, microscopic, or other clinical chemistry markers suggesting liver injury or cholestasis. Although histology studies were limited. All changes related to BMS-986165 were reversible following one month recovery except the mildly increase in WBC in males at the dose of 15mg/kg/day. Three-month study in monkeys showed a moderate increase in transaminases without any microscopic correlation in one of two given BMS-986165 at the dose of 5mg/kg/day at week 17 of the study. The increase was more pronounced for AST compared to ALT. BMS-986165 was found to be not carcinogenic in mice taking a daily dose ≤60 mg/kg/day for six months. Tumors observed in BMS-986165 animals were felt to be incidental, given the lack of dose response, presence in vehicle control groups, and frequent occurrence as a spontaneous finding in this strain of mouse.

3.2.2 Liver Histopathology: During necropsy, only tissues showing gross lesions were evaluated for histopathology. Remaining tissues were formalin fixed and discarded once other testing were negative or when decided that no additional testing was required.

[7] Thomas et al,2004 STAT: A modulator of chemotherapy-induced apoptosis. Cancer research

[8] Che et al, 2015 STAT1 inhibits human hepatocellular carcinoma cell growth through induction of p53 and Fbxw7. Cancer cell International

Overall, animal studies did not show significant liver injury or carcinogenicity risk, though histologic examinations of the liver were limited for the former. DEUC effects on STAT1 may theoretically effect cancer risk.

4.0 Clinical data

4.1 In class or near class DILI data: Marketed JAKis have been associated with mild-to-moderate transient serum aminotransferase elevations and hepatitis B reactivation. JAKis approved for other chronic inflammatory conditions include tofacitinib (JAK1/3 inhibition predominant), upadacitinib (JAK1 inhibition predominant), and baricitinib (JAK1/2 predominant) (Table 1). The labels include liver enzyme elevations in the warnings and precautions. LiverTox® reported these three JAKis as associated with hepatitis B reactivation [9,10,11] and transient, mild elevations in serum aminotransferase, but they have yet to be linked to cases of clinically apparent acute liver injury[12].

Table 3: JAK inhibitors and DILI Related Label Content

JAKi	Boxed Warning	Warnings & Precautions include liver enzyme elevations	Indication (approval year)
Tofacitinib	• Lymphoma and other malignancies • Thrombosis	Yes	PsA (2017)
Upadacitinib	"	"	PsA (2021)
Baricitinib	"	"	RA (2018)

Source: DILI Team

DEUC is the first proposed TYK2 inhibitor for PsO. The proposed label states DEUC is not recommended in patients with severe hepatic impairment (Child-Pugh C) based on hepatic impairment pharmacokinetic studies. The proposed label does not include the JAKis boxed warnings, and warnings and precautions listed in Table 3.

4.2 Summary of Studies:

The total safety population included PsO subjects from two double blinded randomized placebo and active controlled phase 3 studies (Studies IM011046 and IM011047) and the open-label extension study (IM011075) and a phase 2 study (Study IM011011), and psoriatic arthritis (PsA) subjects from a phase 2 study IM011084 (Table 4). The safety evaluation of DEUC focuses on the integrated safety analysis sets (ISS: including Studies IM011046, IM011047 and IM011075) and a 120-day safety update of ISS. Figures 1-4 show study schematics for the phase 2 and 3 studies.

[9] Chen, Y-M, et al. Ann Rheum Dis (2018) https://ard.bmj.com/content/77/5/780.long
[10] FDA, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211675Orig1s000MedR.pdf
[11] Harigai, M, et al. RMD Open (2020) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7046961/
[12] LiverTox: https://www.ncbi.nlm.nih.gov/books/NBK574351/, accessed on July 14, 2022

In total, the PsO program has 1950 safety subjects who received at least one dose of treatment, including 267 from the phase 2 study and 1683 from the two phase 3 studies.

Table 4: Clinical Studies in PsO Subjects

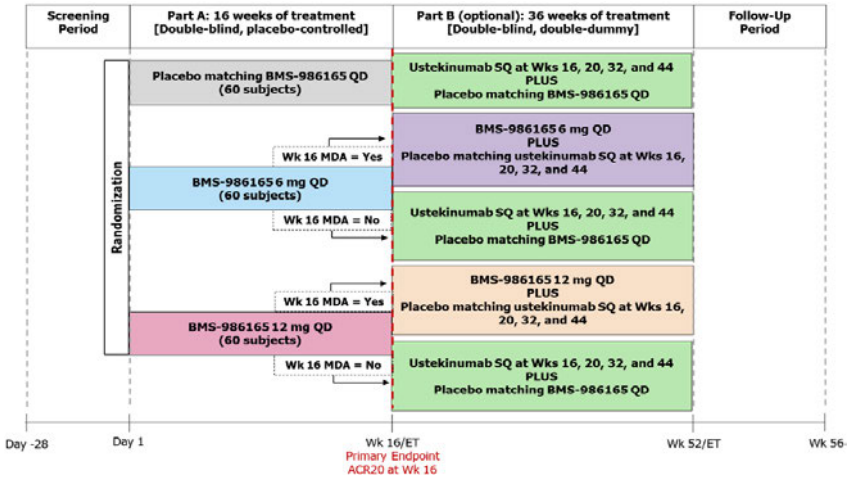
Study	Phase	Design and Duration	Disease; N	Placebo or AC
IM011084	2	R (1:1:1), DB, PBO and AC	PsA; 203	Yes
IM011011	2	R (1:1:1:1:1:1), DB, PBO, 5 doses	PsO; 267	Yes
IM011046	3	52-week study, R (2:1:1), DB: • DEUC: 52-wk • PBO: 16-wk, switched to 38-wk DEUC • AC: 24-wk; non-RESP by PASI 50: 30-wk DEUC, and RESP: AC.	PsO; 665	Yes
IM011047	3	52-week study, R (2:1:1), DB: Period 1: 16-wk PBO, 24-wk DEUC, 24-wk AC Period 2: • PBO: re-R to 38-wk DEUC • DEUC/AC non-RESP by PASI 75: 30-wk DEUC • DEUC RESP: re-R to DEUC and PBO (1:1). PBO relapse switched to DEUC • AC RESP: PBO first, DEUC after relapse	PsO; 1018	Yes
IM011075	3	OLE	PsO; 1221	No

DB = double blind; AC = active comparator (apremilast); IR = inadequate response; OLE = open label extension; PBO = placebo; PASI = psoriasis area and severity score; R = randomized; re-R = re-randomization; RESP = responders.

Source: DILI team

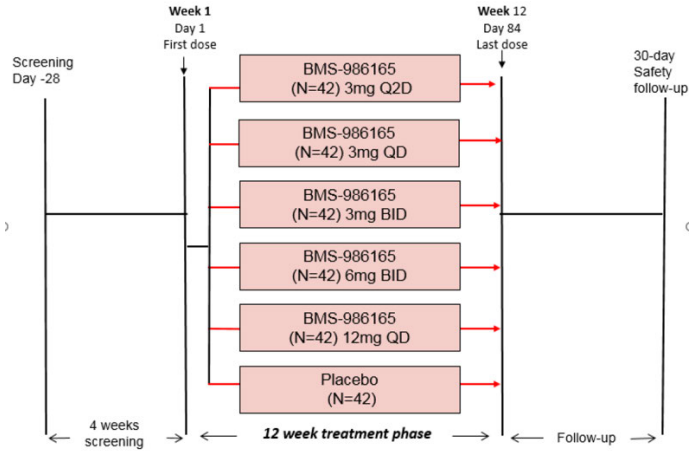
We show the schematics for the phase 2 and 3 studies in Figures 5-8.

Figure 5 Study IM011084 Design Schematic



Source: Study IM011084 CSR Page 26

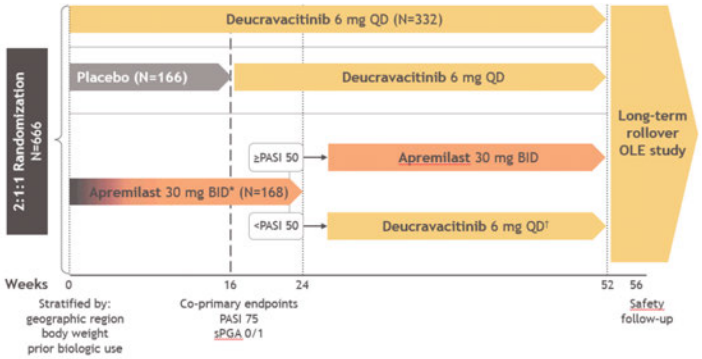
Figure 6: Study IM011011 Design Schematic



Abbreviations: BID = twice daily; N = total number of subjects; Q2D = every other day; QD = once daily

Source: Phase 2 Study IM011011 CSR Page 38

Figure 7: Study IM011046 Design Schematic

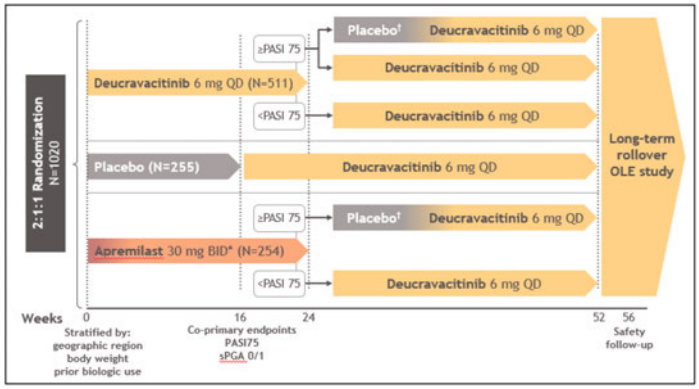


*Apremilast is titrated from 10 mg QD to 30 mg BID over the first 5 days of dosing, as described in Section 4.1.2 of the protocol (Appendix 1.1). The co-primary endpoints will be evaluated at Week 16.

Abbreviations: BID - twice daily; PASI 50 - at least 50% reduction from baseline in the Psoriasis Area and Severity Index; QD - once daily; R - randomize.

Source: Phase 3 Study IM011046 CSR Page 30

Figure 8: Study IM011047 Design Schematic



*Upon relapse (at least a 50% loss of Week 24 PASI percent improvement from baseline), subjects were switched to BMS-986165 6 mg QD.

†Apremilast was titrated from 10 mg QD to 30 mg BID over the first 5 days of dosing.

Abbreviations: Abbreviations: BID = twice daily; OLE - open label extension; PASI = Psoriasis Area and Severity Index; QD = once daily

Source: Phase 3 Study IM011047 CSR Page 38

4.3 Phase 3 studies design features related to DILI evaluation: The two DB phase 3 studies had the same inclusion and exclusion criteria, but different study designs.

Inclusion criteria: Subjects with moderate-to-severe PsO and who were candidates for systemic or phototherapy; adults ≥ 18 years of age; PASI ≥ 12, sPGA ≥ 3, BSA involvement ≥ 10%.

Exclusion criteria: ALT and/or AST >3 × ULN; and/or total unconjugated and/or conjugated bilirubin >2 × ULN. Hepatitis B (HBV) or hepatitis C (HCV) infection, human immunodeficiency virus (HIV) infection, or tuberculosis.

Study designs:

Study IM011046: 2:1:1 randomization to DEUC, placebo and apremilast (n = 332:168:165). Subjects randomized to DEUC stayed on DEUC for 52 weeks. The placebo arm included 16-week placebo then 38-week DEUC. At Week 24, those initially randomized to apremilast were categorized as responders and non-responders by PASI cut-off of 50. Responders stayed on apremilast. Non-responders switched to DEUC until Week 52. Period 1 was the double blind treatment period from baseline to Week 16 for those who received placebo, and to Week 24 for those received DEUC or apremilast.

Study IM011047: Period 1 included 2:1:1 randomization to the DEUC, placebo, and apremilast (n = 510:254:254). Period 2: Subjects randomized to placebo were to be switched to DEUC at Week 16. Subjects initially randomized to DEUC who did not achieve PASI 75 at Week 24, remained on DEUC or were switched to DEUC at Week 24. Subjects initially randomized to apremilast who did not achieve PASI 75 at Week 24 were switched to DEUC 6 mg QD. Period 2 also includes a randomized treatment withdrawal phase: at Week 24, subjects initially randomized to DEUC 6 QD who were responders (≥ PASI 75) were rerandomized (1:1) to DEUC 6 mg QD or placebo. Once first predefined relapse occurred (≥ 50% loss of Week 24 PASI improvement from baseline), subjects were to be switched to DEUC 6 mg QD (Week 24 -52). Subjects initially randomized to apremilast who were responders (≥ PASI 75) were switched to placebo. Analogously to DEUC week-24 responders who switched to placebo, these apremilast week-24 responders received DEUC once relapse occurred.

Some notable comparisons between the two Phase 3 studies:

- Study completers for both studies rolled over to the OLE study.
- Subjects initially randomized to placebo were treated the same in both studies.
- Study 11047 was larger (1020 versus 665 subjects) and more complex in adaptive design compared to Study 11046.

- Subjects randomized to DEUC stayed on DEUC throughout study 11046, but in 11047 DEUC subjects underwent reassignment and re-randomization with treatment withdrawal in some, based on response.
- Subjects randomized to apremilast were reassigned based on treatment response in 11046, but in 11047 subjects were both reassigned and re-randomized with treatment withdrawal in some, based on response.

4.4 Study Level Findings relevant to DILI

4.4.1 Phase 2 PsO study (IM011011, n = 267): No subject met the Hy's law criteria in this study. No subjects had jaundice case or ALT > 3 x ULN. There was no more than mild TEAEs associated with DILI or hepatic disorders during the study. This is reasonable given the limited sample size.

4.4.2 Phase 2 PsA study (IM011084, n = 203): No subject met the Hy's law criteria in this study. No subjects had jaundice. One DEUC subject had ALT and AST > 5 x ULN with competing cause of myopathy. DEUC was resumed after transaminase levels returned to normal. There was no report on TEAEs associated with DILI or hepatic disorders during the study. This is reasonable given the limited sample size.

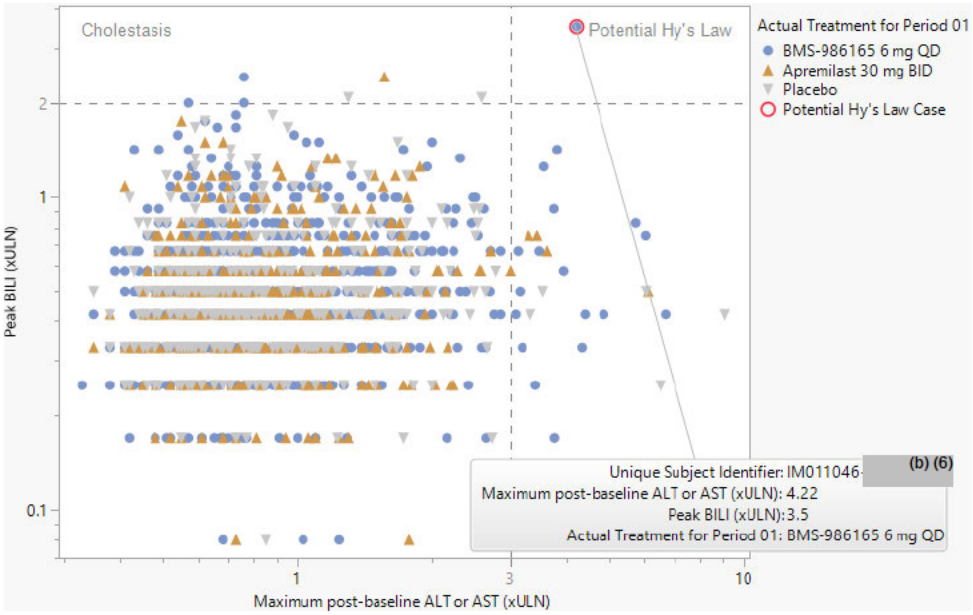
4.4.3 Phase 3 PsO study IM011046 (N = 665): Overall, the eDISH plot identified two potential Hy's law cases (Figure 5). The CSR considered these two cases as not due to DILI and reported few mild hepatic TEAE. However, the CSR's liver related biochemistry results (Table 8.7.2.1-1) appeared inconsistent with our findings based on the laboratory data (ADLB dataset). We issued an IR on April 7, 2022. Based on the adaptive study design, the IR requested a summary of key biochemical data surrounding the study level DILI signal in the DEUC arm against that in placebo and apremilast arms during two periods: 1) Weeks 0-16 to compare DEUC with placebo; 2) Weeks 0-24 to compare DEUC with apremilast.

1). <u>Study 11046</u> Weeks 0 to 16:

Weeks 0-16 results reported higher percentage of DEUC subjects with ALT, AST and BILI elevations than those received placebo or apremilast (Table 5). The eDISH plot shows one DEUC subject met the potential Hy's law criteria (Figures 9 and 10). The sponsor correctly concluded that the case in the Hy's law quadrant was associated with a more likely alternative etiology (alcohol). The Temple's corollary quadrant confirms presence of more DEUC subjects compared with than placebo and apremilast subjects (higher ALT or AST values along the x-axis). As shown in Figures 9 and 10, AST measures accounted for much of the imbalance in

transaminase elevations. This is consistent with the findings in Table 3.

Figure 9 Study IM011046: Overall eDISH Plot (weeks 0-16)



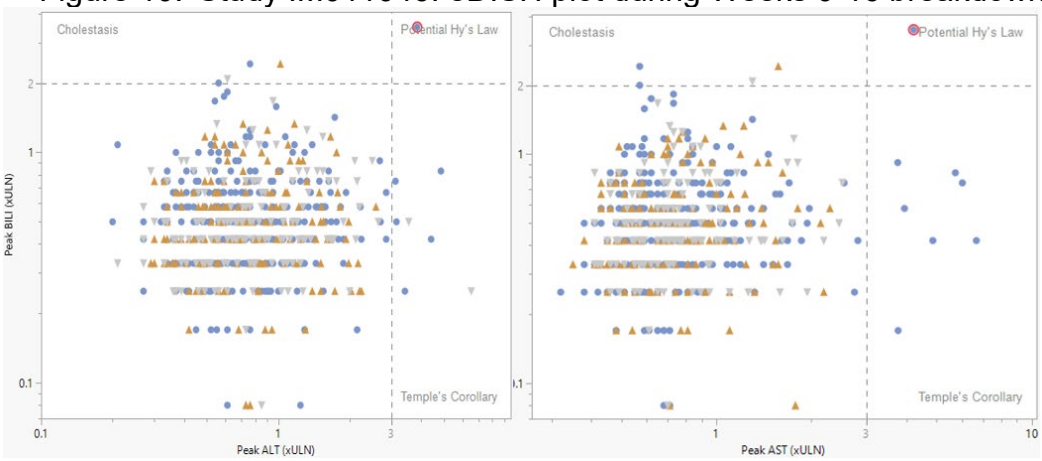
Source: DILI team

Table 5: Study IM011046 Liver Biochemistry results in Weeks 0-16

Week 0-16	Study 046			Study 047		
	DEUC N = 332	Apremilast N = 168	Placebo N = 165	DEUC N = 510	Apremilast N = 254	Placebo N = 254
ALT						
≥ 3 x ULN	6 (1.8%)	0	2 (1.2%)	3 (0.6%)	3 (1.2%)	3 (1.2%)
≥ 5 x ULN	0	0	1 (0.6%)	0	0	2 (0.8%)
AST						
≥ 3 x ULN	8 (2.4%)	0	0	5 (1.0%)	3 (1.2%)	2 (0.8%)
≥ 5 x ULN	3 (0.9%)	0	0	0	0	1 (0.4%)
BILI ≥ 2 x ULN	3 (0.9%)	1 (0.6%)	1 (0.6%)	1 (0.2%)	0	1 (0.4%)
ALP ≥ 2 x ULN	0	0	0	0	0	0

Source: DILI team adaptation based on IR response dated April 28, 2022

Figure 10: Study IM011046: eDISH plot during Weeks 0-16 breakdown



Source: DILI team

2). Study 11046 Weeks 0 to 24:

Weeks 0-24 comparison also shows apparently greater percentage of DEUC subjects experienced ALT and AST elevations comparing to apremilast arm (Table 6). The eDISH plot confirmed this imbalance (Figure 11). Here again the AST elevations accounting for much of the difference particularly at the >5x ULN threshold.

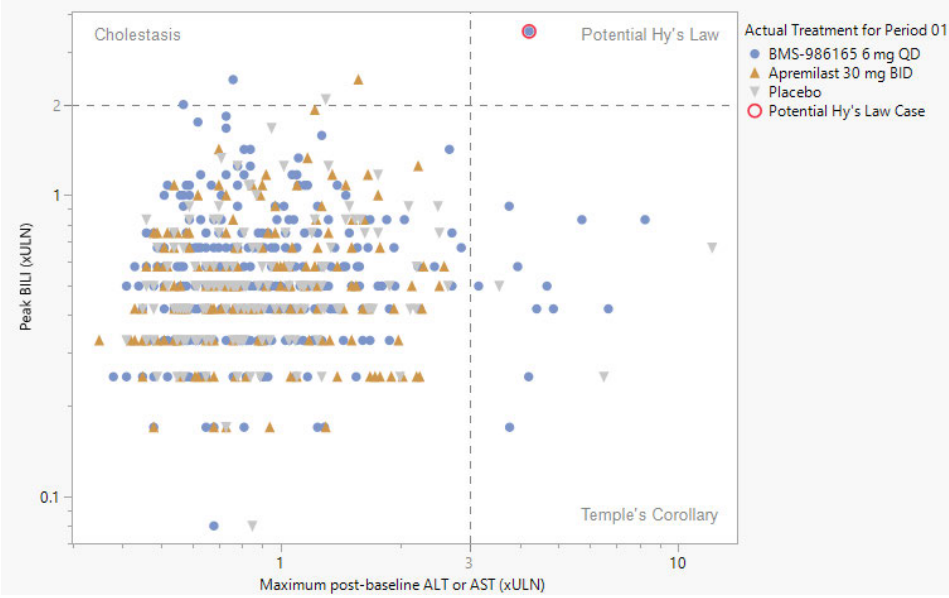
Note that case level assessment refers to Section 4.5 below.

Table 6: Study IM011046 Liver Biochemistry results in Weeks 0-24

Week 0-24	Study 046		Study 047	
	DEUC N = 332	Apremilast N = 168	DEUC N = 510	Apremilast N = 254
ALT				
≥ 3 x ULN	7 (2.1%)	0	4 (0.8%)	3 (1.2%)
≥ 5 x ULN	0	0	1 (0.2%)	0
AST				
≥ 3 x ULN	9 (2.7%)	0	5 (1.0%)	3 (1.2%)
≥ 5 x ULN	3 (0.9%)	0	0	1 (0.4%)
BILI ≥ 2 x ULN	3 (0.9%)	1 (0.6%)	2 (0.4%)	0
ALP ≥ 2 x ULN	0	0	0	0

Source: DILI team adaptation based on IR response dated April 28, 2022
Source: DILI team

Figure 11: Study IM011046: eDISH Plot during Weeks 0-24

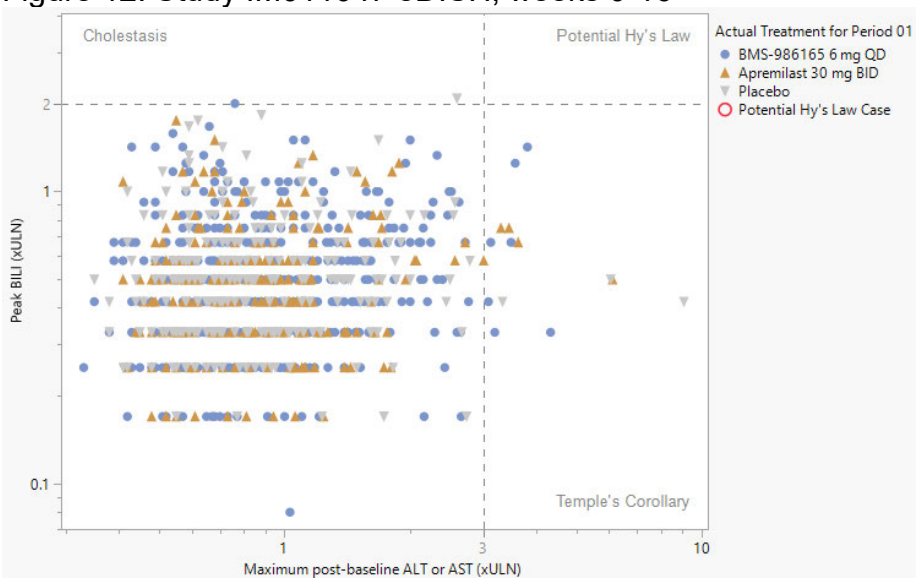


Source: DILI team

4.4.4 Phase 3 PsO study (IM011047, n = 1018): The CSR stated there were DILI concerns for this study, but the Temple's corollary quadrant appears balanced across treatment arms during the first 16 and 24 weeks (Figures 12 and 13). With the adjustment of the randomization ratio, Tables 3 & 4 above reported higher percentages of ALT and AST elevations in the placebo and apremilast arms in comparison to the DEUC arm. This paradox might be due to chance. The sample size of the smaller IM01146 erroneously detected a small difference that was not seen in the larger IM011047 study (i.e., suggestive of a Type I error in the smaller study).

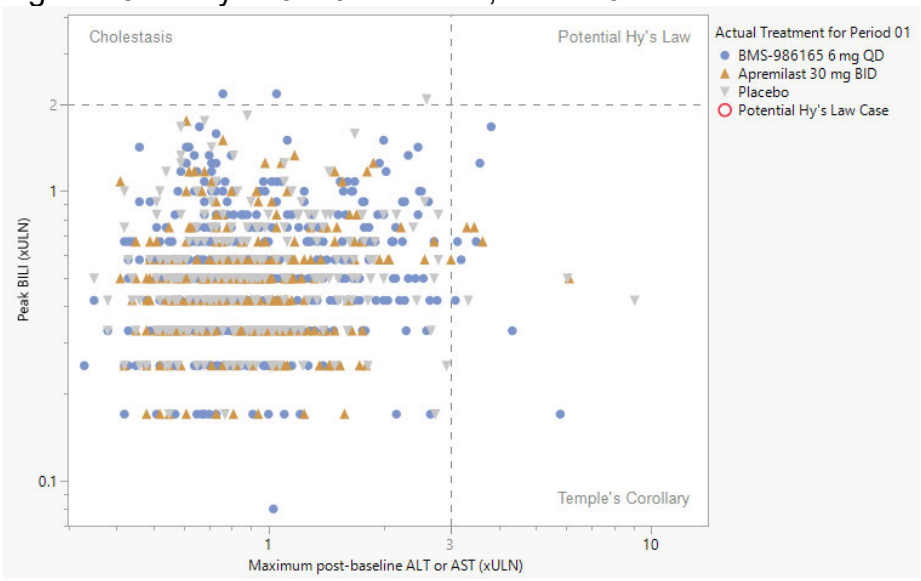
Note that the CSR reported one death of DEUC subject (ID: IM011047-[redacted] (b) (6)) with hepatocellular carcinoma (HCC) diagnosed on Day 224 of the study. The sponsor considered the death unrelated to DEUC. We discuss this case in Section 4.5.

Figure 12: Study IM011047 eDISH, weeks 0-16



Source: DILI team

Figure 13: Study IM011047 eDISH, weeks 0-24



Source: DILI team

4.4.5 ISS (Studies IM011046 and IM011047, n = 1683): Given their identical inclusion and exclusion criteria, it is acceptable to pool the two pivotal phase 3 studies to increase powering for hepatic injury evaluation, especially during the first 16- and 24-week periods. Table 8 summarizes the liver transaminase and BILI elevation across treatment arms by Week 16 and 24. By Week 16, DEUC subjects have the highest AST elevation (1.5%, ≥ 3 x ULN) among all subjects. By Week 24, subjects received DEUC clearly

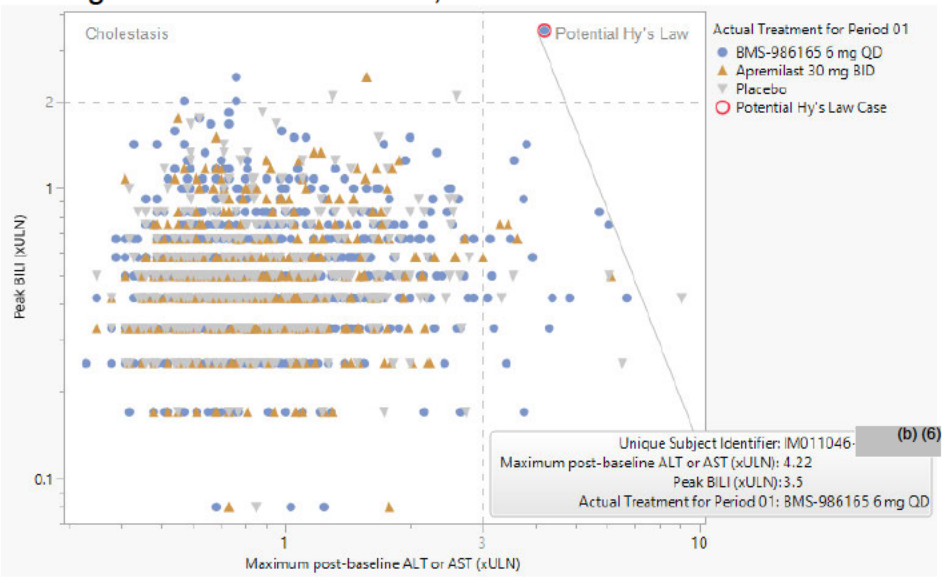
experienced more ALT, AST and BILI elevation relative to apremilast subjects, though the difference for ALT was not sustained at >5x ULN. (Table 7) Note that the exposure time is not adjusted for the percentage calculation here since the dropout rates were low during the first 24 weeks. ISS eDISH plots for weeks 0-16 and 0-24 are shown in Figures 14 and 15.

Table 7: ISS Liver Biochemistry Results

	ISS: Studies 046 and 047				
	Week 0-16			Week 0-24	
	DEUC N = 842	Apremilast N = 422	Placebo N = 419	DEUC N = 842	Apremilast N = 422
ALT					
≥ 3 x ULN	9 (1.1%)	3 (0.7%)	5 (1.2%)	11 (1.3%)	3 (0.7%)
≥ 5 x ULN	0	0	3 (0.7%)	1 (0.1%)	0
AST					
≥ 3 x ULN	13 (1.5%)	3 (0.7%)	2 (0.5%)	14 (1.7%)	3 (0.7%)
≥ 5 x ULN	3 (0.4%)	0	1 (0.2%)	3 (0.4%)	1 (0.2%)
BILI ≥ 2 x ULN	4 (0.5%)	1 (0.2%)	2 (0.5%)	5 (0.6%)	1 (0.2%)
ALP ≥ 2 x ULN	0	0	0	0	0

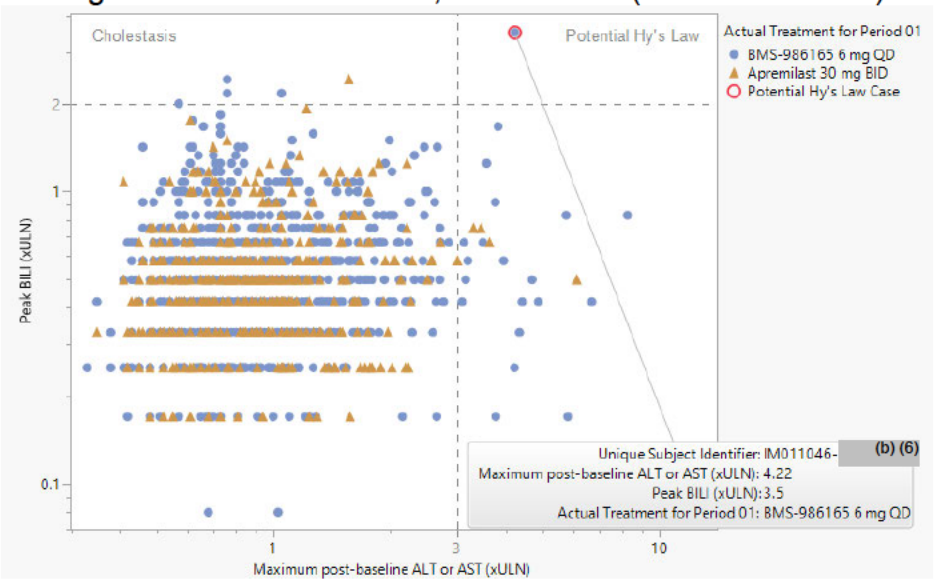
Source: DILI team adaptation based on IR response dated April 28, 2022

Figure 14: ISS eDISH Plot, Weeks 0-16



Source: DILI team

Figure 15: ISS eDISH Plot, Weeks 0-24 (No Placebo Arm)



Source: DILI team

Overall, there were higher percentages of subjects with ALT >3x ULN in the DEUC arms compared to apremilast and placebo, but this difference did not continue at >5x ULN. For AST the differences did persist at >5x ULN but more modestly (+0.2% differences) than at >3x ULN.

120-day safety update (DSU) on ISS: This update submission included ADLB and ADEX datasets for the 3 PsO studies. There were 30 subjects had ALT or AST >= 5 x ULN and related AEs. These are consistent with the overall P3 study results by Week 52. The second IR was issued in June 2022 to obtain case level data for liver related cases identified during the analysis of liver biochemistry data and/or with serious AEs (HCC, etc).

4.5 Case level analyses: We assessed 27 subjects with transaminase levels greater than 5x ULN or >3x ULN with TB >2x ULN or cases identified as having a liver related SAE. None were considered probable DILI. One had possible DILI due to DEUC with competing etiologies of non-alcoholic fatty liver (NAFLD) and/or alcoholic fatty liver disease (AFLD). One subject had a rapidly progressive liver cancer, and its rapid progression may have been related to DEUC. The remaining 25 were considered unlikely related to DEUC.

Of the 25 unlikely DILI subjects, the most common alternate diagnosis was myopathy or myositis (9 subjects) which is atypical. In the DILI Team's experience, myopathy or myositis are not common competing diagnoses. The next most common was "unknown" (six subjects) which is typical in our experience. There were four subjects with NALFD and/or AFLD, three with

DILI from another agent, two with gallstone disease and one with CMV infection as alternate diagnoses.

We highlight three subjects below:

1. Subject (b) (6) (Study 11046): DDD and eDISH plotting identified this subject as potentially meeting Hy's Law, but we think the cause of liver injury was more likely alcohol with underlying Gilberts. We assessed this case as unlikely DILI.

Summary: This is a 41-year-old Asian man with PsO.

At baseline, he had "moderate fatty liver by sonogram." He also had "alcohol dependence." His ALT was 110 U/L, AST 80 U/L, TB 0.9-1.2 mg/dL, AP 88 U/L at baseline. There was no other past medical history given.

He started DEUC 6 mg/day on (b) (6). On (b) (6), his liver enzymes and TB rose to ALT 119, AST 119, AP 90, TB 4.2 mg/dL (no bilirubin fractionation). No symptoms are mentioned. The investigator stopped DEUC on (b) (6) (Day 58).

On (b) (6), enzymes rose further to peak at ALT 158, AST 156, AP 92, but TB fell to 2.0 mg/dL (no fractionation).

Evaluation testing is unclear. The narrative states, "no other immediately apparent possible causes of liver function test elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, preexisting chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic", but specific test results are not given. There was still no fractionation of bilirubin. The narrative says the diagnosis was "confounded by alternative etiologies (alcohol dependence, fatty liver, ALT and AST elevated to ≥ 2x ULN at screening and baseline, and bilirubin at ULN at screening)." Thereafter his liver tests returned to near his baseline. (Table 8)

Table 8: Liver biochemistries by study day

	LFT-US					
		ALP	LDH	ALT	AST	BILI
	Units	U/L	U/L	U/L	U/L	mg/dL
	Range	40-129	0-250	0-41	0-37	0-1.2
	Day-28	98	284	82	86	1.2
DEUC 6 mg/d	Day1	88	256	110	80	0.9
	Day8	92	287	82	97	1
	Day15	93	267	101	113	1.9
	Day29	90	278	82	96	2
	Day58	98	292	119	119	4.2
	Day62	92	249	158	156	2.6
	Day92	93	176	101	74	1.5

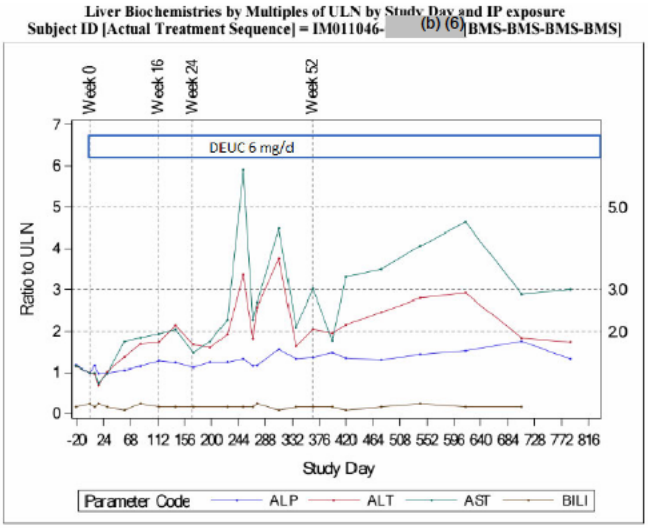
Assessment: This is unlikely DILI due to DEUC. Latency and modest dechallenge are supportive of DILI, but the level of injury is mild when comparing peak TA levels to the subject's baseline (1.5 to 2 x baseline). The rise in TB is out of proportion (3.5 x ULN) the TA elevations, and inconsistent with acute DILI. There was no fractionation of the TB. This case fits better with alcohol related fatty liver with Gilberts.

2. Subject (b) (6) (Study 11046): We felt this subject had possible DILI due to DEUC, but alcohol and non-alcoholic fatty liver disease compete.

Summary: This is a 45-year-old white woman with PsO.

At baseline, she had a history of jaundice possibly due to hepatitis A in (b) (6), but ALT remained elevated thereafter. Her BMI was 32.3 kg/m^2 and she was diagnosed with "hepatic steatosis" in (b) (6). It is unclear if biopsy was done for diagnosis. The narrative gives no history of alcohol use. She took acetaminophen (APAP) (b) (6), but no other concomitant medications. At baseline: ALT 65 U/L, AST 44, AP 114, TB 0.3 mg/dL.

She started DEUC 6 mg/d on (b) (6). During (b) (6), she took APAP (500 mg q 6 hours) for an URI. On (b) (6), her ALT was 219, AST 260, AP 151. No other new medications were taken within 6 months prior to this rise. She had no other symptoms. Her liver enzymes remained modestly elevated over baseline, but TB remained normal. DEUC continued to censor date of (b) (6). CPK and LDH were not elevated. No evaluation testing was done. No symptoms mentioned. DEUC continued without change in dose. (Figure 16)
Figure 16:



Assessment: We considered this case as only possible DILI due to DEUC. The overall rise and lack of return to baseline while on DEUC could be a chronic DILI with only partial or stuttering tolerance. Onset could be when initial rise at around day 50, making latency more consistent with DILI. However, worsening NALFD or alcohol liver injury would fit this injury pattern well if weight increased during this time and/or occult alcohol use occurred. Without jaundice and only possible attribution to DEUC, we do not see this case as a significant concern for approval or labeling.

3. Subject (b) (6) (Study 11047):

Summary: This is a 54-year-old Asian man with PsO.

At baseline, he had a history of diabetes, latent TB (treated) and hepatitis C (? Treated). Former smoker (16 pk-yr) and denied alcohol. At baseline: ALT 21, AST 21, AP 107 TB 0.3.

He started DEUC 6 mg/d on (b) (6). Liver enzymes and TB remained normal or minimally elevated through study day 197. On (b) (6) (b) (6) (Day 209), AFP was 851 ug/L (normal <20-30 ug/L). There is no information on why AFP was checked, and no prior values provided. A CT on (b) (6), showed cirrhosis, portal hypertension, varices, and ascites. The portal, splenic and superior mesenteric veins were all thrombosed. However, no mass was seen on that scan. On (b) (6), he had a variceal bleed. EGD "revealed scarring from prior banding" in the distal esophagus and grade 2 varices. Colonoscopy showed a "mass on the liver". It is unclear if this is a typo or if there was external compression on the colon by a liver mass. On (b) (6), an MRI showed a 5 cm "malignant neoplasm" in the right lobe with "enhancement on the portal venous phase." DEUC was stopped on (b) (6), due to these findings. By (b) (6), AFP was up to 1327 ug/L. Endoscopic ultrasound examination and biopsy of peri-hepatic lymph nodes showed poorly differentiated carcinoma, and no pancreatic mass.

The subject went on "immunotherapy" on (b) (6), but this was stopped by (b) (6), due to rapid clinical decline and futility considerations. The subject died (b) (6), due to advanced hepatocellular carcinoma.

Assessment: This liver injury is not hepatoxicity due to DEUC. The hepatocellular carcinoma (HCC) is likely due to background cirrhosis due to hepatitis C. Implicating DEUC causing cirrhosis is not plausible with normal liver enzymes throughout course of treatment, and no evidence for a chronic DILI similar to methotrexate. Total exposure was 223 days only.

Cirrhosis likely due to hepatitis C was longstanding and explains the HCC occurence. Prior banding and AFP check suggest clinicians knew of the cirrhosis. Whether DEUC increased the risk of HCC progression and portal system thrombosis is plausible, but impossible to prove definitely. We do not have prior liver imaging or prior AFP values. Five of 6 approved JAKi's are labeled for thrombosis risk and 4 of 6 labeled for malignancy. In sum, we DEUC did not lead to HCC in this case, but rapid progression and thrombosis may have been enhanced as seen in one case report.[13]

5.0 Assessment & Recommendations

5.1 **Assessment**: Deucravacitinib (DEUC) is a small molecule, Janus kinase (JAK) inhibitor, targeting the JAK, TYK2. DEUC is taken orally. Like other JAK inhibitors, DEUC blunts the effects of several cytokines including interleukins and interferons, but differs by having a different target, the pseudokinase domain. Whether this difference translates into a better safety profile is unknown. The labels for at least three other JAK inhibitors, mention liver enzyme elevations in their warnings and precautions, but none have liver injury as a box warning.

Non-clinical data for DEUC do not suggest a significant risk of DILI. The drug is rapidly absorbed and hepatically metabolized via CYP1A2, 2B6, 2D6 and 3A4, but no glutathione binding metabolites were found. The majority of DEUC and its metabolites are excreted via bile and feces. In vitro studies suggest, the parent compound, which is predominant, can inhibit BSEP. Inhibition of MRP2 was much less. We found no mitochondrial toxicity studies. Animal studies did not suggest liver histopathologic damage though microscopic examinations were limited to targeted lesions only. We found no data for carcinogenicity in the animal studies, though inhibition of STAT1 has been seen in some cancers.

The ISS included 1683 subjects exposed to DEUC across two Phase 3 studies. While there was an increase in subjects with ALT > 3x ULN compared to apremilast (1.3% versus 0.7%) during weeks 0 to 24, we did not see such a difference compared to placebo during weeks 0 to 16. Moreover, there were no significant differences at ALT > 5x ULN. The differences for AST did persist for AST >5x ULN but this may be due to myopathy rather than DILI. We assessed almost all cases with significant ALT or AST elevation as unlikely DILI, and myopathy was the most common alternate explanation. No case meeting biochemical criteria for Hy's Law (i.e., transaminases > 3x ULN and TB >2 x ULN) was attributable to DILI. Thus, there were no Hy's Law cases.

[13] Migita R, et al. Case Reports in Rheumatology, 2022

Subjects with evidence of hepatitis B infection were excluded from the DEUC phase 3 trials, so reactivation risk could not be addressed. However, approved JAK inhibitors have been associated with reactivation.

The only subject of concern was a man who died of rapidly progressive hepatocellular carcinoma (HCC) with significant thromboses of his portal, splenic and mesenteric veins. He likely had cirrhosis from hepatitis C so development of HCC cannot be attributed to DEUC. However, a case of HCC rapid progression has been reported in a patient taking baricitinb followed by tofacitinib for rheumatoid arthritis.[14] "Lymphoma and other malignancies" and "deep venous thromboses" are boxed warnings for at least three approved JAK inhibitors.

In summary, there is no DILI risk found that would hold up approval. One fatality due to rapidly progressive HCC is noteworthy and may warrant mention in the label. Labeling for hepatitis B reactivation risk similar to other JAK inhibitors may also be warranted.

5.2 **Recommendations:**

1. Do not hold up approval for hepatotoxicity risk concerns.
2. Liver enzymes and bilirubin should be checked at baseline, and when clinically indicated thereafter.
3. While subjects with positive hepatitis B serologies were excluded in the pivotal trials, consider labeling for hepatitis B reactivation risk, similar to other JAK inhibitors.
4. Consider inclusion of a description of the DEUK-treated subject who developed rapidly progressive HCC in the product label as a reminder for physicians to follow hepatocellular carcinoma (HCC) screening guidelines when DEUK is used in patients with cirrhosis or who are otherwise at increased risk for HCC.
5. Consider labeling of malignancy and thrombosis risk similar to other JAK inhibitors.
6. Post-market evaluation should include identification and characterization of any new cases of HCC and portal system thromboses in subjects with cirrhosis, and hepatitis B reactivation.

Paul H. Hayashi -S
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Date: 2022.08.01 15:18:19 -04'00'
(PHH signing for Dr. Lan)

Ling Lan, MD, PhD
Clinical Analyst, DILI Team, Division of Hepatology and Nutrition
CDER/OND

[14] Migita R, et al. Case Reports in Rheumatology, 2022

Paul H. Hayashi -S

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Date: 2022.08.01 15:19:17 -04'00'

Paul H. Hayashi, MD, MPH
DILI Team Lead, Division of Hepatology and Nutrition
CDER/OND

Joseph G. Toerner -S

Digitally signed by Joseph G. Toerner -S
Date: 2022.08.02 09:16:53 -04'00'

Joseph Toerner, MD, MPH
Director, Division of Hepatology and Nutrition
CDER/OND

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PAUL H HAYASHI
08/02/2022 09:51:00 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 20, 2022
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 214958
Product Name and Strength:	Sotyktu (deucravacitinib) tablet, 6 mg
Applicant/Sponsor Name:	Bristol-Myers Squibb Company
OSE RCM #:	2021-1817-1
Acting DMEPA 1 Team Leader:	Madhuri R. Patel, PharmD
DMEPA 1 Associate Director for Nomenclature and Labeling:	Mishale Mistry, PharmD, MPH

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on June 1, 2022 for Sotyktu. Division of Dermatology and Dentistry (DDD) requested that we review the revised container labels and carton labeling for Sotyktu (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

3 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

[a] Patel, M. Label and Labeling Review for deucravacitinib (NDA 214958). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 MAR 09. RCM No.: 2021-1817.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MADHURI R PATEL
07/20/2022 10:15:56 AM

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DIVISION OF CARDIOLOGY AND NEPHROLOGY

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Subject: On September 10, 2021, Bristol Myers Squibb Company submitted a new 505(b)(1) NDA 214958 for deucravacitinib (b) (4) oral tablets. This is an NME under review for the proposed indication - treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

Sponsor: Bristol Myers Squibb Company

Drug Product: BMS 986165 (deucravacitinib, (b) (4)

Date received: February 2, 2022

Date Completed: May 31, 2022

1. Background and Consult Request

The sponsor has submitted a New Drug Application (NDA) for deucravacitinib for the treatment of patients with moderate-to-severe plaque psoriasis. Deucravacitinib is a small molecule that inhibits tyrosine kinase 2 (TYK2), thereby inhibiting type I interferons (IFN), interleukin (IL)-23, and IL-12 which are involved in the initiation and pathogenesis of psoriatic disease.

According to the Applicant, deucravacitinib is a selective TYK2 inhibitor that binds to the pseudokinase domain of TYK2, distinct from the kinase domain binding site for ATP-competitive Janus Kinase (JAK) inhibitors. However, TYK2 is considered a JAK (Janus kinase) isoform, and

JAK inhibitors have a Boxed Warning for major adverse cardiovascular events (MACE), and thromboembolic events.

The sponsor has submitted two phase 3, 52-week, randomized, placebo- and active-controlled studies to support efficacy and safety of deucravacitinib in adult subjects with moderate-to-severe plaque psoriasis. Given the epidemiologic association between psoriasis and cardiovascular (CV) comorbidities, and the purported mechanism of action of deucravacitinib, potential CV adverse events (AEs) in the two pivotal studies were adjudicated by a blinded committee of external cardiovascular experts (CV Adjudication Committee). The CV adjudication committee (CVAC) concluded that there was no increased risk of MACE or thromboembolic events with deucravacitinib.

The Consult Request states that, "*MACE, extended MACE, and thrombotic events have been reported during deucravacitinib' s clinical development program; however, after the clinical reviewer grouped terms e.g., myocardial infarction, acute myocardial infarction, coronary artery occlusion, troponin I increased, angina pectoris, blood creatine phosphokinase increased, blood creatine phosphokinase MB increased, myocardial ischemia, coronary artery disease coronary artery stenosis, arteriosclerosis coronary artery, angina unstable, and cardiac arrest based on FMQs, an imbalance of incidence rates for these CV events was not apparent between treatment groups during the controlled trials.*

During the open-label long-term extension trial, 7 subjects had events of MACE or extended MACE, 4 of whom were less than 50 years of age. One subject was a 35-year-old woman with no apparent CV risk factors who had an ischemic stroke. Another subject was a 37-year-old man with limited CV risk factors who had unstable angina requiring hospitalization…..

….The clinical reviewer's assessment thus far has not identified a signal for myocarditis, myopericarditis, or elevated troponin I levels. The reviewer's analyses did identify an imbalance of pericarditis and atrial fibrillation although confounding comorbidities (e.g., COVID-19, recent CABG, prior history of atrial fibrillation, mitral valve incompetence, and acute CHF) make attribution difficult to determine for these adverse events.

(b) (4)

The Division of Dermatology and Dental Products (DDD) requests the following input from the Division of Cardiology and Nephrology (DCN):

1) Are the Applicant's search and analyses adequate for assessing the cardiovascular safety for this product?
2) Do you agree with the CV Adjudication Committee's analyses?
3) Please advise on whether you would recommend additional data/analysis specific to deucravacitinib in the treatment of psoriasis to better assess/describe cardiovascular safety.
4) Please provide your assessment as to whether labeling of pericarditis and/or atrial fibrillation is warranted.

5) Please provide your assessment as to whether class labeling for JAK inhibitors is appropriate.

2. Materials Reviewed:

1) NDA 203214 Tofacitinib (Relevant portions)
    a. Summary of Clinical Safety
    \\CDSESUB1\evsprod\nda203214\0000\m2\27-clin-sum\summary-clin-safety.pdf

2) NDA 214958 (Relevant Portions)
    a. Summary of Clinical Safety
    \\CDSESUB1\evsprod\nda214958\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\psoriasis\5353-rep-analys-data-more-one-stud\iss\summary-clin-safety-bms986165-pso-initial.pdf

    b. Proposed Label for Deucravacitinib
    \\CDSESUB1\evsprod\nda214958\0023\m1\us\init-nda-pso-deucr-markup-medguide-29apr22.pdf

    c. Cardiovascular End Points Adjudication Charter/ Clinical Study Report IM011046 link

    d. Sponsor Response to FDA IR dated March 11, 2022, here

    e. Sponsor Response to FDA IR dated May 4, 2022, here

    f. Sponsor Response to FDA IR dated May 9, 2022, here
    \\CDSESUB1\evsprod\NDA214958\0031

    g. Sponsor Response to FDA IR dated May 13, 2022
    \\CDSESUB1\evsprod\NDA214958\0029

    h. Sponsor Response to FDA IR dated May 19, 2022
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3) FDA Label for Tofacitinib (JAK inhibitor)

4) FDA Label for Apremilast (Otezla)

3. Clinical Review

3.1. Deucravacitinib Proposed Label

Relevant portions of the proposed label for deucravacitinib are listed below:

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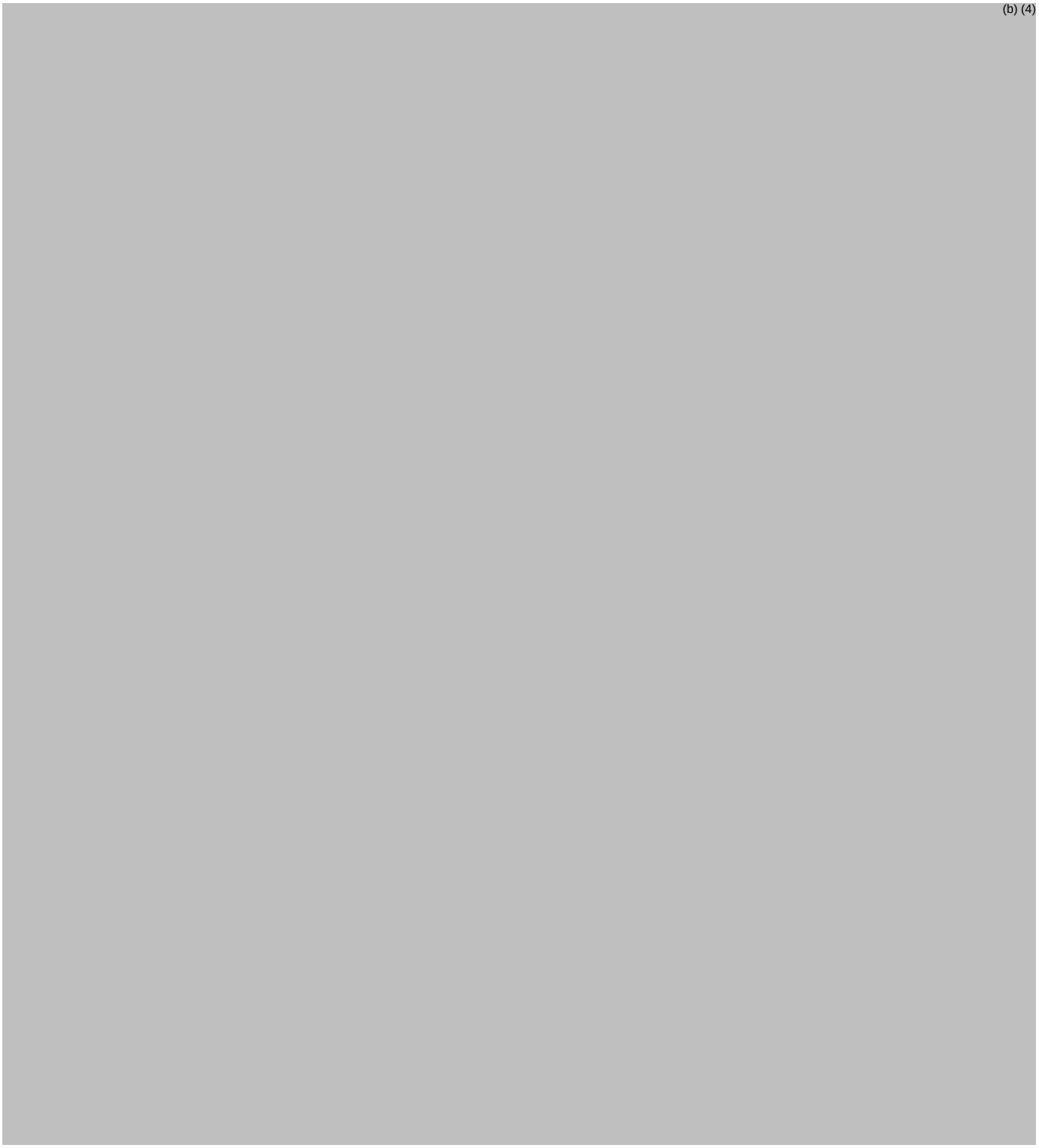

Reviewer Comments: *Deucravacitinib' s unique mode of binding is thought to render high selectivity for TYK2 without inhibiting Janus kinase (JAK)1, JAK2, or JAK3. The proposed label does not describe any increase in incidence of CV or thrombo-embolic adverse events associated with deucravacitinib.*

3.2. Cardiovascular Safety of JAK Inhibitor – Tofacitinib

Tofacitinib (Xeljanz) was initially approved in 2012. It is currently indicated to treat patients with rheumatoid arthritis (RA), psoriatic arthritis (PA), ankylosing spondylitis (AS), ulcerative colitis (UC), polyarticular course juvenile idiopathic arthritis who have had an inadequate response or intolerance to one or more TNF blockers.

Tofacitinib is a potent, selective inhibitor of the Janus kinase (JAK) family of kinases. In kinase assays, tofacitinib inhibits JAK1, JAK2, JAK3, and to a lesser extent tyrosine kinase 2 (TyK2). In cellular settings where JAK kinases signal in pairs, tofacitinib preferentially inhibits signaling by heterodimers containing JAK3 and/or JAK1 with functional selectivity over JAK2 homodimer signaling. Inhibition of JAK1 and JAK3 by CP-690,550 blocks signaling through the common gamma chain containing receptors for several cytokines, including interleukin (IL)-2, -4,-7,-9, -15 and -21. These cytokines are integral to lymphocyte activation, proliferation, and function, and inhibition of their signaling may thus result in modulation of multiple aspects of the immune response. In addition, inhibition of JAK1 will result in attenuation of signaling by additional pro-inflammatory cytokines, such as IL-6 and interferon (IFN). At higher exposures, inhibition of erythropoietin signaling could occur via inhibition of JAK2 homodimer signaling.

RA Safety Study
In December 2021, tofacitinib received a boxed warning for a higher incidence of MACE and thrombosis compared to TNF blockers in RA patients based on post-approval RA Safety Study. The Safety Study was a randomized, open label, active-control study that randomized patients with RA, 50 years or older with at least one CV risk factor to tofacitinib 5 mg twice daily (N-1455), tofacitinib 10 mg twice daily (N=1456), and TNF-blocker (N=1451). The co-primary endpoints were adjudicated MACE (defined as cardiovascular death, non-fatal MI, and non-fatal stroke) and adjudicated malignancy (excluding non-melanoma skin cancer); the study was designed to exclude a prespecified risk margin of 1.8 for the hazard ratio of combined tofacitinib regimens versus the TNF-blocker control for each co-primary endpoint. An independent committee conducted a blinded evaluation of the co-primary endpoints according to predefined criteria (adjudication). The study was event driven and patients were followed until a sufficient number of primary outcome events accrued. Other endpoints included mortality, serious infections, and thromboembolic events. The median on-study follow-up time was 4.0 years.

The mean age of the trial population was 61 years (range: 50 to 88 years). Most patients were female (78%) and Caucasian (77%). Patients had a diagnosis of RA for a mean of 10 years, and a median swollen and tender joint count of 11 and 15 respectively. CV risk factors included cigarette smoking (current or past) (48%), hypertension (66%), high density lipoprotein < 40 mg/dL (12%), diabetes mellitus (17%), family history of premature coronary heart disease (15%), extra-articular disease associated with RA (37%), and history of coronary artery disease

(11%). The non-inferiority criterion was not met for the primary comparison of the combined tofacitinib doses to TNF blockers since the upper limit of the 95% CI exceeded the pre-specified non-inferiority criterion of 1.8 (for MACE, the upper limit of the 95% CI was 1.94; for malignancies excluding NMSC, the upper limit of the 95% CI was 2.09).

Table 1 shows results of the RA Safety Study.

Table 1 Results of RA Safety Study 1 (Source: Tofacitinib [Xeljanz] FDA Label)

Endpoint	XELJANZ 5 mg Twice Daily N=1455 PY=5490	XELJANZ 10 mg Twice Daily N=1456 PY=5298	TNF Blocker N=1451 PY=5468
MACE, n [IR]	50 [0.91]	59 [1.11]	43 [0.79]
HR (95% CI)*	1.16 (0.77, 1.74)	1.41 (0.95, 2.10)	
MI,† n [IR]	20 [0.36]	21 [0.39]	11 [0.20]
HR (95% CI)*	1.81 (0.87, 3.79)	1.97 (0.95, 4.09)	
Stroke,† n [IR]	18 [0.33]	21 [0.39]	20 [0.36]
HR (95% CI)*	0.89 (0.47, 1.69)	1.08 (0.59, 2.00)	
Cardiovascular Death, n [IR]	18 [0.32]	25 [0.47]	15 [0.27]
HR (95% CI)*	1.20 (0.60, 2.37)	1.71 (0.90, 3.24)	
Malignancies Excl. NMSC, n [IR]	62 [1.13]	60 [1.13]	42 [0.77]
HR (95% CI)*	1.47 (1.00, 2.18)	1.48 (1.00, 2.19)	
Malignancies Excl. NMSC (among current and past smokers)††	41 [1.53]	48 [1.91]	25 [0.99]
HR (95% CI)*	1.55 (0.94, 2.55)	1.94 (1.19, 3.14)	
All Death	49 [0.88]	66 [1.23]	38 [0.69]
HR (95% CI)*	1.29 (0.84, 1.96)	1.79 (1.20, 2.66)	
Serious Infections	155 [2.95]	184 [3.65]	133 [2.52]
HR (95% CI)*	1.17 (0.93, 1.47)	1.44 (1.15, 1.80)	
DVT	12 [0.22]	15 [0.28]	9 [0.16]
HR (95% CI)*	1.33 (0.56, 3.15)	1.72 (0.75, 3.92)	
PE	10 [0.18]	26 [0.49]	3 [0.05]
HR (95% CI)*	3.32 (0.91, 12.08)	8.95 (2.71, 29.56)	
VTE	18 [0.33]	36 [0.68]	12 [0.22]
HR (95% CI)*	1.50 (0.72, 3.10)	3.10 (1.61, 5.96)	
ATE	51 [0.93]	55 [1.04]	45 [0.83]
HR (95% CI)*	1.13 (0.76, 1.69)	1.26 (0.85, 1.87)	
TE	67 [1.23]	86 [1.65]	56 [1.03]
HR (95% CI)*	1.19 (0.84, 1.70)	1.60 (1.14, 2.23)	

Note: XELJANZ 10 mg twice daily was discontinued by the Data Monitoring Committee due to safety concerns, and ongoing patients switched from XELJANZ 10 mg to XELJANZ 5 mg. The column "XELJANZ 10 mg Twice Daily" includes all events and follow-up for patients randomized to XELJANZ 10 mg twice daily.A XELJANZ/XELJANZ Oral Solution 10 mg twice daily (or a XELJANZ XR 22 mg once daily) dosage is not recommended for the treatment of RA or PsA *[see Dosage and Administration (2.2)]*.
N indicates number of patients; n indicates number of patients with events.
IR indicates incidence rate per 100 person-year (PY).

Note that the mechanism by which tofacitinib increases risk for cardiovascular and thrombotic events is not well understood.

Some non-CV adverse reactions with tofacitinib include serious infections, malignancy and lymphoproliferative disorders, gastrointestinal perforations, and laboratory abnormalities including lipid elevations.

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3.4. Deucravacitinib Safety Data

3.4.1. Non-Clinical Cardiovascular Safety Risk with Deucravacitinib

Per DDD review team, nonclinical data for deucravacitinib demonstrated myocardial inflammation during the One-month Oral Toxicity Study in Monkeys, however, this finding was not seen during the 3-month and 9-month monkey studies. Additionally, in the 1-month monkey study, two control animals also developed minimal subacute myocardial inflammation. According to the PharmTox reviewer, even if the lower dose of 1.5 mg/kg/day that was studied is considered to be the NOAEL, the exposure margin at this NOAEL dose would be approximately 9.3-times compared to the clinical exposure. There is no animal data suggesting whether deucravacitinib could exacerbate pre-existing myocardial inflammation.

3.4.2. Exposure to Deucravacitinib in Patients with Psoriasis

The following studies contributed to safety experience with deucravacitinib in patients with psoriasis:

- 1 completed phase 2 dose-finding study (IM011011)
- 1 completed phase 2 study in patients with psoriatic arthritis (IM011084, Part A)
- 2 completed pivotal phase 3 studies (IM011046, IM011047)
- 1 ongoing, open-label extension phase 3 study (IM011075)
- 2 ongoing, regional phase 3 studies:
    - A 52-Week randomized placebo-controlled study in China, South Korea, and Taiwan (IM011065); and
    - A single-arm, open-label study in Japan (IM011066)

In addition, there are 16 completed clinical pharmacology studies in healthy volunteers and 2 clinical pharmacology studies in subjects with hepatic impairment.

As of June 15, 2021, there were 9 ongoing blinded studies of deucravacitinib to support non-psoriasis indications such as psoriatic arthritis, systemic lupus erythematosus, Crohn's disease, ulcerative colitis, lupus nephritis, discoid lupus erythematosus, etc.

Table 2 summarizes the exposure to deucravacitinib in patients with psoriasis or psoriatic arthritis.

Table 2. Deucravacitinib Exposure in Patients with Psoriasis / Psoriatic Arthritis

Study	Study Design	Study Arms	Exposure
IM011011 (Phase 2)	12-Week, randomized, placebo-controlled, dose-ranging study in patients with psoriasis.	1:1:1:1:1:1 randomization to deucravacitinib 3mg EOD, 3mg QD, 3 mg BID, 6 mg BID, 12 mg QD or placebo	Total randomized and treated: 267 Treated with deucravacitin b: 222
IM011084 (Phase 2)	16-Week (Part A) randomized, placebo-controlled study in subjects with psoriatic arthritis.	1:1:1 randomization to deucravacitinib 6mg QD or 12 mg QD or placebo.	Total randomized and treated: 203 Treated with deucravacitin b: 137
IM011046 (Phase 3)	52-Week randomized, double-blind, placebo- and active-controlled study in patients with psoriasis.	2:1:1 randomization to deucravacitinib 6 mg QD , placebo or apremilast 30 mg BID. At Week 16, subjects randomized to placebo were switched to deucravacitin b. At Week 24, subjects randomized to apremilast were switched to deucravacitinib if they did not achieve PASI 50.	Total randomized and treated: 665 Treated with deucravacitin b: 531
IM011047 (Phase 3)	52-Week randomized, double-blind, placebo- and active-controlled study in patients with psoriasis.	2:1:1 randomization to deucravacitinib 6 mg QD, placebo or apremilast 30 mg BID. At Week 16, subjects randomized to placebo were switched to deucravacitin b. Randomized Treatment Withdrawal Phase: At Week 24, subjects randomized to deucravacitin b who achieved a PASI ≥ 75 were re-randomized in 1:1 ratio to deucravacitinib or placebo. If subjects experience a relapse, they were switched back to deucravacitin b (Week 24 to 52). Subjects initially randomized to apremilast who achieved PASI ≥ 75 were switched to placebo, and those who did not achieve PASI 75 at Week 24 were switched to deucravacitinib. Subjects initially randomized to deucravacitin b who did not achieve PASI 75 at Week 24 remained on deucravacitinib.	Total randomized and treated: 1018 Treated with deucravacitin b: 833
IM011075 (Phase 3b)	Open-label, single-arm study to evaluate long-term safety and efficacy of deucravacitin b in patients with psoriasis.	Single arm - deucravacitinib	Total randomized and treated with deucravacitin b: 1221 Ongoing treatment: 1099 Discontinued: 122
Abbreviations: PASI, Psoriasis area and severity index			

In the three phase 3 studies, a total of 1519 subjects were exposed to at least one dose of 6 mg once daily of deucravacitinib with a total exposure of approximately 2167 patient-years; 1317 subjects exposed for at least 26 weeks, 1141 for at least 52 weeks, and 296 subjects for at least 104 weeks. The mean and median durations of exposure to deucravacitinib were 521.0 and 588.0 days, respectively.

In the two pivotal controlled phase 3 studies, a total of 1364 subjects were exposed to at least one dose of 6 mg once daily of deucravacitinib with a total exposure of approximately 969 patient-years.

The pivotal phase 3 trials (IM011046 and IM011047) met the pre-specified trial success criteria to demonstrate efficacy of deucravacitinib in patients with psoriasis. For this consult, efficacy data were not reviewed. Only pertinent CV safety data for deucravacitinib in the two pivotal phase 3 trials are reviewed here.

Apremilast (Otezla), used as an active comparator in phase 3 studies, is a phosphodiesterase-4 (PDE4) inhibitor approved to treat patients with psoriatic arthritis, psoriasis and Behcet's Disease. Per FDA Label for apremilast, the three most common adverse reactions reported in ≥ 1% of patients on apremilast (N=506) and with greater frequency than placebo (N=920) included diarrhea, nausea and upper respiratory tract infection. There are no CV AEs described with apremilast in the Label.

Reviewer Comments: *In pivotal phase 3 trials of deucravacitinib, there were a total of 1364 patient exposed to at least one dose of 6 mg once daily of deucravacitinib with a median follow-up duration of 588 days with approximately 969 patient-years of exposure. Whereas in RA Safety Study there were 2911 patients exposed to tofacitinib with a median follow-up of 4 years with approximately 10,788 patient-years of exposure.*

3.4.3. Applicant's Overall Approach to Safety Analysis

The Applicant analyzed safety data for deucravacitinib using as-treated approach in following two data pools:

1) Controlled Safety Pool that included subjects who received at least 1 dose of study drug in the pivotal phase 3 studies – IM011046 and IM011047.

2) Phase 3 Safety Pool that included subjects who received at least 1 dose of study drug in the pivotal phase 3 studies (IM011046, IM011047), and were then enrolled in the ongoing open-label study (IM011075) until the safety cut-off date of June 15, 2021.

Controlled Safety Pool: Safety data from the Controlled Safety Pool were analyzed over 3 different time periods because the treatment group assignments were changed at Weeks 16 and 24, as described in Table 2. The time periods are listed below:

1) Placebo-controlled Period (Week 0-16) based on initial randomized treatment groups.

2) Apremilast-controlled Period (Week 0-24) based on continuously treated patients randomized to deucravacitinib or apremilast (As-Treated Population). Patients who were switched from placebo to deucravacitinib were excluded.
3) Deucravacitinib Exposure Period (Week 0-52) based on continuously treated patients randomized to deucravacitinib or apremilast (As-Treated Population). Patients who were switched from placebo to deucravacitinib were excluded.

3.4.4. Cardiovascular Safety of Deucravacitinib – Applicant's Analysis

Controlled Safety Pool (IM011046 and IM011047 studies)

CV related eligibility criteria: IM011046 and IM011047 studies **excluded** the following patients at increased risk for adverse CV events:

- Unstable CV disease, defined as a recent clinical CV event (e.g., unstable angina, myocardial infarction, stroke, rapid atrial fibrillation) in the last 3 months prior to screening, or a cardiac hospitalization (e.g., revascularization procedure, pacemaker implantation) within 3 months prior to screening.

- Uncontrolled arterial hypertension characterized by a systolic blood pressure (BP) >160 mm Hg or diastolic BP >100 mm Hg.

- New York Heart Association Class III or IV congestive heart failure

Reviewer Comments: *In pivotal phase 3 trials of deucravacitinib, patients at increased risk for CV events were excluded. Whereas RA Safety Study was enriched for adverse CV events by enrolling patients 50 years or older with at least one CV risk factor.*

Cardiovascular Adjudication Committee (CVAC): Given the epidemiologic association between psoriasis and CV comorbidities, cardiac and thrombo-embolic events were **pre-specified as adverse events of interest** (AEIs). Major adverse cardiovascular events (MACE) was defined as non-fatal myocardial infarction, non-fatal stroke or cardiovascular death. Extended MACE (EMACE) was defined as MACE and unstable angina requiring hospitalization.

Serious adverse events (SAEs) in phase 3 trials of deucravacitinib were adjudicated by a blinded committee of external CV experts (CVAC). Table 3 lists SAEs adjudicated by the CV Adjudication Committee.

Table 3 Serious Adverse Events Adjudicated by the CV Adjudication Committee in Phase 3 Trials of Deucravacitinib

Serious Adverse Events Adjudicated by the CV Adjudication Committee
Fatal Case; Death due to: • Myocardial infarction (MI): Non-ST elevation (NSTEMI) • MI: ST elevation (STEMI) • Stroke: ischemia • Stroke: hemorrhagic • Heart failure • Sudden death • Pulmonary embolism

Serious Adverse Events Adjudicated by the CV Adjudication Committee
• Cardiovascular (CV) hemorrhage • CV procedure • Other CV cause, specify: • Other non-CV cause, specify
Non-fatal event: • NSTEMI • STEMI • Stroke: ischemic • Stroke: hemorrhagic • Heart failure • Pulmonary embolism • Unstable angina requiring hospitalization • Arrhythmia not associated with ischemia • Transient ischemic attack • Coronary revascularization • Other CV event, specify: • NOT a CV event
Insufficient information to adjudicate

SAEs for adjudication were identified using the following processes:

1) Clinical database search to identify events using Medical Dictionary for Regulatory Activities (MedDRA) coded adverse event fields (Preferred Terms).
2) Sponsor's monthly assessment of all SAEs reported in the clinical database.
3) Additional SAEs identified by CVAC members during dossier review.

After SAEs were identified, supporting documents for each event dossier were collected.

Collection of source documents was considered futile in the following circumstances:

1) Failed 3 attempts to obtain the documents
2) Event occurred at an institution where principal investigator (PI) was not affiliated, and PI made multiple good faith attempts to obtain the documents.

In both circumstances, the PI was to provide a written response that information could not be obtained.

Definitions of CV SAEs to be adjudicated were reviewed and considered reasonable. For the SAEs of MI and unstable angina, the CVAC members were allowed to exercise some clinical judgment in addition to the event definitions to decide based on totality of available information.

Impact of COVID-19 on study conduct included missed visits; a total of 70 subjects missed at least 1 visit in both studies combined. Planned safety analyses were not modified due to COVID-19 related issues.

Patient Disposition and Baseline Characteristics: Table 4 displays end of treatment status by randomized treatment group for 0-16, 0-24, and 16-24 Weeks in IM011046 and IM011047 studies.

Table 4. End of Treatment Status by Randomized Treatment Group Summary, Full Analysis Set, IM011046 and IM011047 studies (Source: Sponsor tables S.1.1, S.1.2; Summary of Clinical Efficacy)

Week 0 through Week 16

Status (%)	BMS-986165 6 mg QD N = 843	Placebo N = 421	Apremilast N = 422	Total N = 1686
RANDOMIZED	843 (100)	421 (100)	422 (100)	1686 (100)
RANDOMIZED BUT NOT TREATED	1 (0.1)	2 (0.5)	0	3 (0.2)
RANDOMIZED AND TREATED	842 (99.9)	419 (99.5)	422 (100)	1683 (99.8)
COMPLETED THE TREATMENT	763 (90.5)	357 (84.8)	362 (85.8)	1482 (87.9)
NOT COMPLETED THE TREATMENT	79 (9.4)	62 (14.7)	60 (14.2)	201 (11.9)
REASON FOR NOT COMPLETING THE TREATMENT				
ADVERSE EVENT	16 (1.9)	14 (3.3)	22 (5.2)	52 (3.1)
DEATH	0	1 (0.2)	1 (0.2)	2 (0.1)
LACK OF EFFICACY	6 (0.7)	10 (2.4)	5 (1.2)	21 (1.2)
LOST TO FOLLOW-UP	12 (1.4)	8 (1.9)	6 (1.4)	26 (1.5)
NON-COMPLIANCE WITH PROTOCOL	6 (0.7)	3 (0.7)	3 (0.7)	12 (0.7)
PREGNANCY	0	0	1 (0.2)	1 (0.1)
SITE TERMINATED BY SPONSOR	0	0	0	0
STUDY TERMINATED BY SPONSOR	0	0	0	0
WITHDRAWAL BY SUBJECT	18 (2.1)	12 (2.9)	12 (2.8)	42 (2.5)
OTHER	21 (2.5)	14 (3.3)	10 (2.4)	45 (2.7)

Week 0 through Week 24

Status (%)	BMS-986165 6 mg QD N = 843	Apremilast N = 422
RANDOMIZED	843 (100)	422 (100)
RANDOMIZED BUT NOT TREATED	1 (0.1)	0
RANDOMIZED AND TREATED	842 (99.9)	422 (100)
COMPLETED THE TREATMENT	742 (88.0)	349 (82.7)
NOT COMPLETED THE TREATMENT	100 (11.9)	73 (17.3)
REASON FOR NOT COMPLETING THE TREATMENT		
ADVERSE EVENT	22 (2.6)	25 (5.9)
DEATH	0	1 (0.2)
LACK OF EFFICACY	11 (1.3)	6 (1.4)
LOST TO FOLLOW-UP	14 (1.7)	8 (1.9)
NON-COMPLIANCE WITH PROTOCOL	9 (1.1)	4 (0.9)
PREGNANCY	1 (0.1)	2 (0.5)
SITE TERMINATED BY SPONSOR	0	0
STUDY TERMINATED BY SPONSOR	0	0
WITHDRAWAL BY SUBJECT	20 (2.4)	14 (3.3)
OTHER	23 (2.7)	13 (3.1)

Week 16 through Week 24

Table 4. End of Treatment Status by Randomized Treatment Group Summary, Full Analysis Set, IM011046 and IM011047 studies (Source: Sponsor tables S.1.1, S.1.2; Summary of Clinical Efficacy)

Status (%)	BMS-986165 6 mg QD N = 762	PBO-BMS-986165 N = 357	Apremilast N = 362
RECEIVED TREATMENT	762 (100)	357 (100)	362 (100)
COMPLETED TREATMENT PERIOD	741 (97.2)	343 (96.1)	349 (96.4)
NOT COMPLETED THE TREATMENT PERIOD	21 (2.8)	14 (3.9)	13 (3.6)
REASON FOR NOT COMPLETING THE TREATMENT PERIOD			
ADVERSE EVENT	6 (0.8)	2 (0.6)	3 (0.8)
DEATH	0	0	0
LACK OF EFFICACY	5 (0.7)	6 (1.7)	1 (0.3)
LOST TO FOLLOW-UP	2 (0.3)	0	2 (0.6)
NON-COMPLIANCE WITH PROTOCOL	3 (0.4)	1 (0.3)	1 (0.3)
PREGNANCY	1 (0.1)	0	1 (0.3)
SITE TERMINATED BY SPONSOR	0	0	0
STUDY TERMINATED BY SPONSOR	0	0	0
WITHDRAWAL BY SUBJECT	2 (0.3)	2 (0.6)	2 (0.6)
OTHER	2 (0.3)	3 (0.8)	3 (0.8)

Baseline demographics and disease characteristics were balanced across treatment groups in Controlled Safety Pool with mean age of 47 years, 10% were ≥ 65 years old, 87% were white, mean body mass index (BMI) was 31 kg/m^2, 31% had hypertension, 10% had hyperlipidemia, and 10% had type 2 diabetes mellitus. Concomitant medication use was generally similar across treatment groups.

Reviewer Comments: *The prevalence of cardiovascular co-morbidities in the Controlled Safety Pool of deucravacitinib phase 3 program is lower than in the RA Safety Study.*

Analysis of Adverse Events: All adverse events (AEs) presented are treatment emergent. Treatment emergent adverse events (TEAEs) are events that occurred after the first dose of study treatment through 30 days after the final dose of the study treatment or subject's participation in the study if the last scheduled visit occurred at a later time.

During the placebo-controlled period (Week 0-16), the overall incidence of AEs in deucravacitinib group (56%) was similar to apremilast and higher than placebo group. The incidence of severe AEs (2%) and serious AEs (2%) in deucravacitinib was generally low, and similar to other treatment groups. The incidence of AEs leading to treatment discontinuation (2%) in deucravacitinib group was lower than other treatment groups. There were 3 deaths, 1 in each treatment group, and none were considered as treatment-related by the investigator.

Deaths: There were 4 deaths in total in Studies IM011046 and IM011047 (2 in the deucravacitinib group – due heart failure and hepatocellular carcinoma; 1 in placebo group – sudden death; and 1 in apremilast group – metastatic lung cancer with gastrointestinal bleed). There were 6 deaths reported in Study IM011075 (as of the June 15, 2021, safety data cutoff date). Five of the 6 deaths in IM011075 were due to COVID-19 and 1 death was attributed to ruptured thoracic aortic aneurysm with hemopericardium.

Tables 5, 6, and 7 summarize Applicant's analysis of investigator reported CV and thromboembolic AEs by treatment group in the three treatment periods in as-treated population in the Controlled Safety Pool.

Table 5 Cardiovascular and Thromboembolic Adverse Events by Treatment Groups in Placebo-Controlled Period (Week 0-16), As-Treated Population, Controlled Safety Pool (IM011046, IM011047) (Applicant's analysis)

Adverse Event (SOC/PT)	Deucravacitinib N = 842	Placebo N = 419	Apremilast N = 422
Incidence Rate (EAIR per 100 patient years)			
AEs Vascular disorders (SOC)	8	3	11
SAEs Vascular Disorders (SOC)	0	0	0
SAEs Cardiac Disorders (SOC)	1	2	1
Hypertension (PT)	6	1	9
Number of SAEs in SOC of Cardiac and Vascular Disorders			
	n	**n**	**n**
Myocardial Infarction	1	0	1
Acute Myocardial Infarction	0	1	0
Angina Unstable	0	1	0
Cardiac Arrest	1	0	0
Cardiac failure	1	0	0
Ventricular tachycardia	1	0	0
Malignant hypertension	1	0	0
Hypertensive Heart Disease	0	1	0
Ischemic stroke	0	0	1
Peripheral arterial occlusion	0	1	0
Total (n)	**5**	**4**	**2**

Abbreviations: EAIR, Exposure Adjusted Incidence Rate per 100 patients years; SOC, System Organ Class; AE, adverse event; SAE, serious adverse event; P-Y, Patient-Years; n, number of years
EAIR values are rounded to the nearest whole number

Reviewer Comments:
Table 5 indicates that exposure adjusted incidence rate of
-AEs in vascular disorders SOC and AE of PT hypertension was higher in deucravacitinib versus placebo group
-SAEs in cardiac SOC were not increased in deucravacitinib versus placebo or apremilast group.
The overall number of CV SAEs is small. The SAE category of cardiac and vascular disorders should reflect the incidence of MACE and extended MACE. In the SAE cardiac disorders category, no AEs of atrial fibrillation or pericarditis were reported by the Applicant.
The AE of increase in blood creatine phosphokinase (CPK) is not specific for cardiac related AEs. Therefore, data on increase in CPK is not included in this review.

Table 6 Cardiovascular and Thromboembolic Adverse Events by Treatment Groups in Apremilast-controlled Period (Week 0-24), As-Treated Population, Controlled Safety Pool (IM011046, IM011047) (Applicant's analysis)

Adverse Event (SOC/PT)	Deucravacitinib N = 842	*Placebo N = 419	Apremilast N = 422
Incidence Rate (EAIR per 100 patient years)			
SAEs Cardiac Disorders (SOC)	2	2	1
Hypertension (PT)	5	1	8
Number of SAEs in SOC of Cardiac and Vascular Disorders			

Adverse Event (SOC/PT)	Deucravacitinib N = 842	*Placebo N = 419	Apremilast N = 422
n			
Myocardial Infarction	1		1
Myocardial Ischemia	1		0
Angina Unstable	1		0
Cardiac Arrest	1		0
Cardiac failure	1		0
Atrial Fibrillation	1		0
Ventricular tachycardia	1		0
Supraventricular tachycardia	1		0
Malignant hypertension	1		0
Ischemic Stroke	0		2
Total (n)	**9**		**3**

Abbreviations: EAIR, Exposure Adjusted Incidence Rate per 100 patients years; SOC, System Organ Class; AE, adverse event; SAE, serious adverse event; P-Y, Patient-Years

EAIR values are rounded to the nearest whole number

*The events in placebo group during the Apremilast-controlled period are similar to Placebo-Controlled Period because switched from placebo to deucravacitin b were excluded.

Reviewer Comments:

Table 6 indicates that exposure adjusted incidence rate of

-AE of hypertension PT was higher in deucravacitinib versus placebo group.

-SAEs in cardiac disorders SOC was similar in deucravacitinib versus placebo group but were slightly higher in deucravacitinib versus apremilast group.

The overall number of CV SAEs is small. Only one SAE of atrial fibrillation is described in deucravacitinib group. No SAE of pericarditis is reported by the Applicant.

Table 7 Cardiovascular and Thromboembolic Adverse Events by Treatment Groups in Deucravacitinib Exposure Period (Week 0-52), As-Treated Population, Controlled Safety Pool (IM011046, IM011047) (Applicant's analysis)

	Deucravacitinib N = 1364	*Placebo N = 419	Apremilast N = 422
Incidence Rate (EAIR per 100 patient years)			
SAEs Cardiac Disorders (SOC)	1	2	1
Hypertension (PT)	4	2	7
Number of SAEs in SOC of Cardiac, Vascular and Respiratory Disorders			
n			
Myocardial infarction	1		1
Unstable Angina	1		0
Cardiac arrest	1		0
Cardiac failure	1		0
Ventricular tachycardia	1		0
Supraventricular tachycardia	1		0
Atrial Fibrillation	2		0
Pericarditis	2		0
Ischemic Stroke	0		2
Cerebrovascular accident	1		0
Aortic dissection	1		0
Malignant hypertension	1		0
Pulmonary embolism	1		0
Total (n)	**14**		**3**

Abbreviations: EAIR, Exposure Adjusted Incidence Rate per 100 patients years; SOC, System Organ Class; AE, adverse event; SAE, serious adverse event; P-Y, Patient-Years
EAIR values are rounded to the nearest whole number
*The events in placebo group during the Deucravacitinib Exposure Period are similar to Placebo-Controlled Period because patients switched from placebo to deucravacitinib were excluded.

Reviewer Comments:

Table 7 indicates that exposure adjusted incidence rate of

-AE of hypertension PT was higher in deucravacitinib versus placebo group.

-SAEs in cardiac disorders SOC was lower in deucravacitinib versus placebo group and similar in deucravacitinib versus apremilast group.

The overall number of CV SAEs is small. Only two SAEs each of atrial fibrillation and pericarditis are reported in deucravacitinib group.

Hypertension

Further analyses revealed that there was no clinically meaningful difference in change from baseline in systolic and diastolic blood pressure in as-treated population, in controlled safety pool in the three treatment groups (table 8).

Table 8 Change from Baseline in Systolic and Diastolic Blood Pressure in Controlled Safety Pool, As-treated Population (Source: Sponsor response to FDA IR dated May 9, 2022)

Week 0 through Week 24

Measurement Test (Units): Systolic Blood Pressure (mmHg)

Period Visit	Trt	Value N	Mean	SD	Min	Q1	Median	Q3	Max	IQR
BASELINE	BMS	835	128.2	13.16	84	120	129	137	179	17
	PBO	416	127.9	12.79	97	119	128	138	163	19
	APR	422	127.5	13.01	94	119	129	136	160	17

Measurement Test (Units): Systolic Blood Pressure (mmHg)

Period Visit	Trt	Value N	Mean	SD	Min	Q1	Median	Q3	Max	IQR	Change From Baseline N	Mean	SE	Median	Min	Max	IQR
WEEK 0 - WEEK 16																	
WEEK 16	BMS	765	127.2	12.66	83	119	128	136	167	17	760	-0.7	0.41	0	-47	54	13
	PBO	362	128.0	13.60	83	119	128	137	172	18	359	0.3	0.60	0	-36	34	13
	APR	369	126.6	13.04	90	119	127	135	170	16	369	-0.8	0.61	0	-38	44	13
WEEK 16 - WEEK 24																	
WEEK 20	BMS	752	127.1	12.54	91	119	127	136	191	17	747	-1.0	0.42	0	-46	37	13
	APR	358	127.6	13.24	90	120	127	136	169	16	358	0.2	0.61	0	-35	41	14
WEEK 24	BMS	735	127.9	12.77	92	120	128	137	182	17	730	0.1	0.44	0	-56	39	14
	APR	350	128.3	13.63	92	119	128	138	187	19	350	0.9	0.64	0	-33	51	14

Measurement Test (Units): Diastolic Blood Pressure (mmHg)

Period Visit	Trt	Value N	Mean	SD	Min	Q1	Median	Q3	Max	IQR
BASELINE	BMS	835	80.7	8.89	54	75	81	87	109	12
	PBO	416	80.2	8.53	57	74	81	86	99	12
	APR	422	80.1	8.66	54	74	80	86	105	12

Measurement Test (Units): Diastolic Blood Pressure (mmHg)

Period / Visit	Trt	Value N	Mean	SD	Min	Q1	Median	Q3	Max	IQR	Change From Baseline N	Mean	SE	Median	Min	Max	IQR
WEEK 0 - WEEK 16																	
WEEK 16	BMS	765	80.3	8.79	55	75	81	86	105	11	760	-0.3	0.31	0	-32	34	10
	PBO	362	80.0	9.12	51	74	81	87	109	13	359	0.0	0.42	0	-26	29	9
	APR	369	79.5	8.83	45	74	80	85	106	11	369	-0.7	0.43	0	-46	23	10
WEEK 16 - WEEK 24																	
WEEK 20	BMS	752	80.1	8.64	52	75	80	86	107	11	747	-0.5	0.31	0	-28	32	11
	APR	358	80.2	9.05	57	74	80	86	117	12	358	0.0	0.43	0	-24	23	10
WEEK 24	BMS	735	80.4	8.77	56	74	81	87	109	13	730	-0.2	0.32	0	-28	39	10
	APR	350	80.4	9.62	54	74	80	87	122	13	350	0.3	0.45	0	-33	28	10

Week 0 through Week 52

Measurement Test (Units): Systolic Blood Pressure (mmHg)

Period / Visit	Trt	Value N	Mean	SD	Min	Q1	Median	Q3	Max	IQR
BASELINE	BMS	325	127.3	13.41	84	119	128	136	179	17
	APR	114	126.3	12.85	94	118	128	136	157	18

Measurement Test (Units): Systolic Blood Pressure (mmHg)

Period / Visit	Trt	Value N	Mean	SD	Min	Q1	Median	Q3	Max	IQR	Change From Baseline N	Mean	SE	Median	Min	Max	IQR
WEEK 52	BMS	268	126.5	12.66	89	119	127	136	163	17	266	-0.5	0.76	0	-42	45	14
	APR	83	126.2	13.00	100	119	125	134	175	15	83	1.2	1.32	1	-25	31	18

Measurement Test (Units): Diastolic Blood Pressure (mmHg)

Period / Visit	Trt	Value N	Mean	SD	Min	Q1	Median	Q3	Max	IQR
BASELINE	BMS	325	80.0	8.88	54	74	80	86	109	12
	APR	114	79.2	9.35	54	73	79	86	98	13

Measurement Test (Units): Diastolic Blood Pressure (mmHg)

Period / Visit	Trt	Value N	Mean	SD	Min	Q1	Median	Q3	Max	IQR	Change From Baseline N	Mean	SE	Median	Min	Max	IQR
WEEK 52	BMS	268	79.7	8.63	52	75	80	86	106	11	266	0.0	0.53	0	-23	27	11
	APR	83	79.2	9.95	56	70	80	85	107	15	83	0.6	0.93	1	-21	23	12

Reviewer's conclusion based on Applicant's analysis:

1) *Based on SAEs presented under cardiac disorders SOC, it cannot be concluded that there is increased risk of MACE with deucravacitinib.*
2) *The incidence of hypertension PT was higher in deucravacitinib versus placebo group, but there was no clinically meaningful change from baseline in blood pressure observed in any treatment group.*
3) *Incidence of arterial and venous thromboembolic events is low to determine an increased risk with deucravacitinib compared to placebo.*
4) *Reviewer performed analysis of adae database of Phase 3 Safety Pool evaluating number of AEs under cardiac and vascular disorder system organ class by preferred term by treatment arm, regardless of severity. These analyses are presented in the Appendix. Reviewer results are generally consistent by the Applicant's results.*

3.4.4.1. Cardiovascular Adjudication Committee and Additional Analyses

Applicant's analysis of adjudicated CV events in As-treated population (including patients switched from placebo to deucravacitinib), regardless of study period, demonstrated the following overall SAEs by group:

Study IM011046

Deucravacitinib: 1 myocardial infarction, 1 atrial fibrillation, 1 ventricular tachycardia, 1 aortic dissection, 2 pericarditis, 1 transient ischemic attack, 1 unstable angina, 1 supraventricular tachycardia (EMACE # 2)

Placebo: 1 myocardial infarction, 1 unstable angina, 1 hypertensive heart disease leading to sudden death (EMACE # 2)

Apremilast: 1 coronary artery occlusion, 1 ischemia stroke (EMACE # 1)

Study IM011047

Deucravacitinib: 1 myocardial ischemia, 2 atrial fibrillation, 1 cerebrovascular accident, 1 worsening atherosclerotic heart disease, 1 malignant hypertension, 1 thrombosis – ischemic clot of right leg, 1 cardiac failure, 1 cardiac arrest (EMACE # 3)

Placebo: 1 pericardial effusion, 1 peripheral artery occlusion (EMACE # 1)

Apremilast: 1 myocardial infarction, 1 ischemic stroke (EMACE # 2)

In response to FDA IR dated May 9 and 13, 2022, the Applicant confirmed that in Controlled Safety Pool:

- a total of 31 SAEs in 28 subjects were reviewed by the CVAC
- of the 31 SAEs, all were adjudicated by the CVAC excepting 1 SAE (supraventricular tachycardia) that could not be adjudicated as dossier did not contain ECG tracings
- of the 31 SAEs reviewed by the CVAC, 5 SAEs were negatively adjudicated with discordance between the PT and the adjudicated term: 3 in the deucravacitinib group and 1 each in the apremilast and placebo groups. Among these discordant adjudicated events, 3 were adjudicated as non- CV events, 1 was adjudicated as a different MACE term, and 1 was adjudicated as part of the primary cause of death and not a separate event
- all cases of MACE and extended MACE (EMACE) were serious and adjudicated by CVAC

Reviewer Comments: *Reviewer analysis of aeadj database of Phase 3 Safety Pool MACE or EMACE were low, generally consistent with the Applicant's results.*

MACE

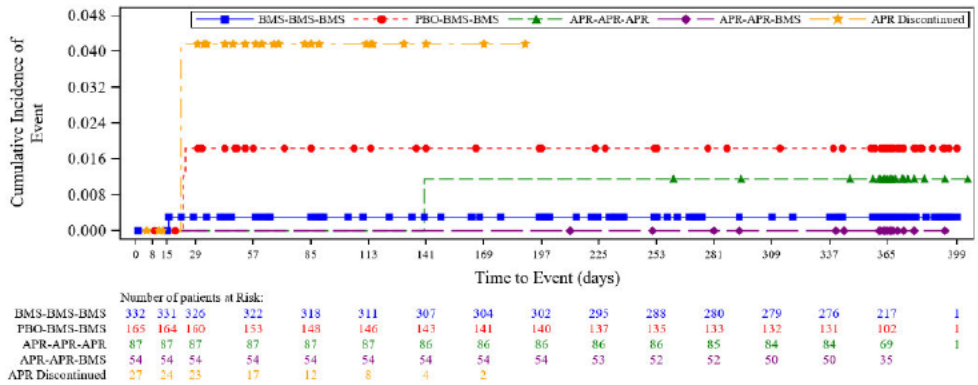
Figure 1 shows the Kaplan-Meier Plots displaying time-to-event and cumulative incidence of MACE in Studies IM011046 and IM011047 by treatment sequence groups. The plots for EMACE appear similar to MACE and are not presented in this review.

Figure 1. Kaplan-Meier Plots for MACE in Studies IM011046 and IM011047 (Source: Sponsor response to FDA IR dated May 9, 2022)

Kaplan-Meier Plots for MACE in Studies IM011046 and IM011047

Figure 6.3.2

Kaplan Meier Plot for Cumulative Incidence of Patients with MACE Event
Week 0 through Week 52
As-treated Population in Study IM011046



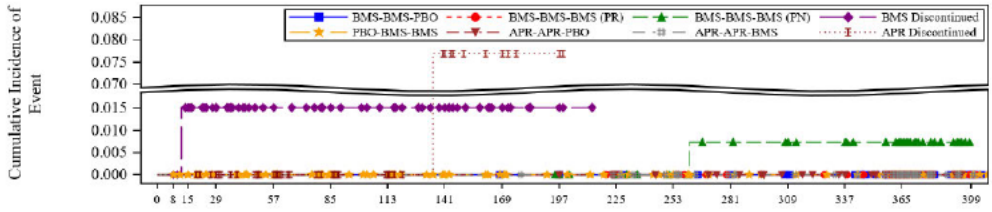
Number of patients at Risk:

BMS-BMS-BMS	332	331	326	322	318	311	307	304	302	295	288	280	279	276	217	1
PBO-BMS-BMS	165	164	160	153	148	146	143	141	140	137	135	133	132	131	102	1
APR-APR-APR	87	87	87	87	87	87	86	86	86	86	86	85	84	84	69	1
APR-APR-BMS	54	54	54	54	54	54	54	54	54	53	52	52	50	50	35	
APR Discontinued	27	24	23	17	12	8	4	2								

Includes events with a start date between first dose and +30 days post last dose date or upon rollover into IM011075.
Subjects are summarized according to treatment sequence. 'APR Discontinued' includes subjects who discontinued prior to treatment switching at Week 24.
Program Source: \\BMSSTATS-BSTATS\SAS\Report\SCS120D\rg-km-ae52-ebr.sas 13MAY2022:15:48:42

Figure 6.3.10

Kaplan Meier Plot for Cumulative Incidence of Patients with MACE Event
Week 0 through Week 52
As-treated Population in Study IM011047



Number of patients at Risk:

BMS-BMS-PBO	150	150	150	150	150	150	150	149	149	148	145	144	142	141	104	3
BMS-BMS-BMS (PR)	148	148	148	148	148	148	148	148	148	146	145	141	141	140	99	3
BMS-BMS-BMS (PN)	142	142	142	142	142	142	142	142	141	138	135	132	130	128	98	
BMS Discontinued	70	64	56	41	33	26	19	10	3							
PBO-BMS-BMS	254	252	245	237	226	219	211	205	202	199	194	189	186	184	138	4
APR-APR-PBO	97	97	97	97	97	97	97	97	97	94	93	91	87	84	62	
APR-APR-BMS	111	111	111	111	111	111	111	111	110	109	105	97	96	94	71	1
APR Discontinued	46	46	42	32	23	17	11	6	2							

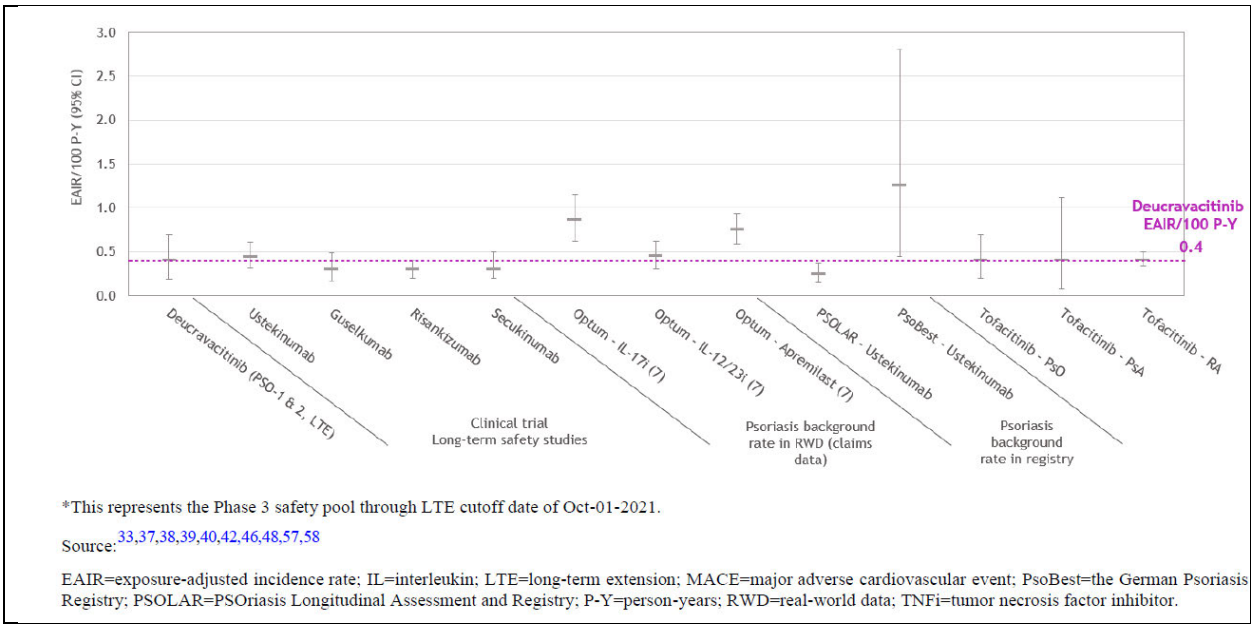
Includes events with a start date between first dose and +30 days post last dose date or upon rollover into IM011075.
Subjects are summarized according to treatment sequence. PR and PN represent PASI75 Responders and Nonresponders at Week 24 (per IRT response), respectively.
'BMS Discontinued' and 'APR Discontinued' include subjects who discontinued prior to treatment switching at Week 24.
Program Source: \\BMSSTATS-BSTATS\SAS\Report\SCS120D\rg-km-ae52-ebr.sas 13MAY2022:15:48:50

Abbreviations: BMS, deucravacitinib; PBO, placebo; APR, apremilast

Reviewer Comments: *The incidence of MACE was low in studies IM011046 and IM011047. The Applicant's results for number of adjudicated MACE and EMACE are similar to reviewer analysis.*
K-M curves for MACE were generated to understand incidence of MACE over time in various treatment groups.
Study IM011046: K-M Curves indicate a lower incidence of MACE in patients on deucravacitinib versus patients who were switched from placebo to deucravacitinib or those on apremilast.
Study IM011047: K-M Curves indicate a lower incidence of MACE in patients on deucravacitinib versus patients who were discontinued from deucravacitinib but slightly higher than the patients on other treatment sequences. The incidence of MACE appears to increase after about 250 days of treatment. This raises some concern about CV safety of long-term use of deucravacitinib. But the number of MACE is low to definitively conclude an increased CV risk with deucravacitinib.

In response to FDA IR dated March 11, 2022, the Applicant also evaluated and reported EAIR for overall MACE in long-term safety studies in patients with moderate to severe plaque psoriasis, with 6 mg once daily dose of deucravacitinib to be 0.4 with 95% CI of 0.2-0.7 (n=9, N=1519, exposure 2482 Patient-Years), and with 5 and 10 mg doses of tofacitinib combined to be 0.4 with 95% CI of 0.2 to 0.7 (n=11, N = 807, Exposure 2705 Patient-Years). For this analysis, deucravacitinib safety data was derived from Studies IM011046, IM011047, and IM011075. There were 3 cases of MACE (1 nonfatal MI and 2 nonfatal strokes) from Study IM011075. Figure 2 displays the EAIR for MACE with deucravacitinib at 2 years compared with long-term safety data, real-world data or registry studies of other systemic psoriasis treatments. The background rate of MACE in patients with psoriasis from claims database is similar to or higher than that observed with deucravacitinib.

Figure 2 EAIRs for MACE with Deucravacitinib at 2 years* compared with long-term safety data, real-world data or registry studies of other systemic psoriasis treatments (Source: Sponsor Figure 4, Response to FDA IR dated 03/11/2022)



*This represents the Phase 3 safety pool through LTE cutoff date of Oct-01-2021.

Source:[33,37,38,39,40,42,46,48,57,58]

EAIR=exposure-adjusted incidence rate; IL=interleukin; LTE=long-term extension; MACE=major adverse cardiovascular event; PsoBest=the German Psoriasis Registry; PSOLAR=PSOriasis Longitudinal Assessment and Registry; P-Y=person-years; RWD=real-world data; TNFi=tumor necrosis factor inhibitor.

The Applicant concluded that there is no increased risk for CV or thrombotic events associated with deucravacitinib and proposes pharmacovigilance activities to ensure safety of patients and continued assessment of risks and their mitigation.

Reviewer Comments: *In patients with psoriasis, the EAIR of MACE with deucravacitinib is similar to that observed with tofacitinib. The EAIR of MACE with tofacitinib in RA Safety Study was approximately 1 per PY compared to 0.4 per PY in patients with psoriasis. The duration of exposure in RA Safety Study is longer than the available safety studies with deucravacitinib, and patients in RA safety study had a higher prevalence of CV co-morbidities than patients with psoriasis in deucravacitinib studies. Hence, an increased risk of MACE with deucravacitinib should be carefully considered as it is used in patients with CV risk factors and for longer duration than the pivotal studies.*

4. DCN's Consult Response to DDD

Question 1: Are the Applicant's search and analyses adequate for assessing the cardiovascular safety for this product?

DCN Response: The applicant's search and analyses, including responses to FDA IRs are adequate to assess observed cardiovascular safety of deucravacitinib in patients with moderate to severe plaque psoriasis in the two pivotal phase 3 trials.

[Note that the following IR was recommended to the DDD, which was sent, and responses received until 5/25/2022 were reviewed:
Please submit the following data for the Controlled Safety Pool:

1) Total number of SAEs reviewed by the Cardiovascular Adjudication Committee (CVAC)
2) Number of negatively adjudicated SAEs
3) Number of SAEs where the dossier was not available or incomplete and therefore the event could not be adjudicated
4) Number of MACE and extended MACE events that were not categorized as serious, hence did not go to CVAC
5) Number of urgent heart failure visits reported in the controlled-safety pool
6) Kaplan–Meier curves for MACE, extended MACE, and extended MACE + thromboembolic events, both investigator reported and adjudicated]

Question 2: Do you agree with the CV Adjudication Committee's analyses?

DCN Response: The CV Adjudication Committee's analyses are reasonable.

Question 3: Please advise on whether you would recommend additional data/analysis specific to deucravacitinib in the treatment of psoriasis to better assess/describe cardiovascular safety.

DCN Response: The following analyses were requested to further understand the effect of deucravacitinib on CV safety profile:

1) Evaluate the change from baseline is systolic and diastolic blood pressure adjusted for baseline by treatment group for placebo-controlled, apremilast-controlled and deucravacitinib exposure periods in as-treated population (i.e., patients who were continuously exposed to just one treatment, not switched to other treatment).
2) Display as a graph - mean systolic and diastolic blood pressure at all available time points by treatment group in placebo-controlled period.

Results of these additional analyses did not reveal any clinically meaningful effect of deucravacitinib on blood pressure versus placebo or apremilast.

Question 4: Please provide your assessment as to whether labeling of pericarditis and/or atrial fibrillation is warranted.

DCN Response: The number of adverse events of pericarditis and atrial fibrillation is too small to conclude an increased risk with deucravacitinib. Hence, we do not recommend labeling for risk of pericarditis and/or atrial fibrillation with deucravacitinib based on safety data from the two pivotal phase trials of deucravacitinib in patients with moderate to severe psoriasis.

Question 5: Please provide your assessment as to whether class labeling for JAK inhibitors is appropriate.

DCN Response: An assessment of whether labeling for JAK inhibitors also applies to deucravacitinib will depend on the degree of overlap in the mechanism of action of JAK inhibitors and deucravacitinib, contributing to treatment benefit and safety profile, and is beyond the scope of this review. Safety data from the two pivotal phase trials of deucravacitinib in patients with moderate to severe psoriasis does not provide conclusive evidence of an increased risk for major adverse cardiovascular events and thromboembolic events with deucravacitinib versus placebo.

The Applicant proposes to continue cardiovascular (CV) safety evaluation of deucravacitinib through routine pharmacovigilance activities. As of June 15, 2021, there were 9 ongoing blinded studies of deucravacitinib to support non-psoriasis indications such as psoriatic arthritis, systemic lupus erythematosus, Crohn's disease, ulcerative colitis, lupus nephritis, discoid lupus erythematosus, etc. The controlled safety data from these ongoing trials will provide additional information on the safety profile of deucravacitinib.

In the preamble to section 6, consider stating that the approximately 969 patient-years of exposure to deucravacitinib in the pivotal phase 3 trials was in a low cardiovascular risk population.

5. Appendix

Table 9 Cardiac and Vascular Adverse Events by Preferred Term in Safety Population During Treatment Period Week 0 to 16

				Week 0 up to Week 16	
				EPOCH	
	BLINDED TREATMENT			FOLLOW-UP	
			TRTA		TRTA
AETERM	Apremilast 30 mg BID	BMS-986165 6 mg QD	Placebo	BMS-986165 6 mg QD	Placebo
ARTERIAL HYPERTENSION	1	1	0	0	0
ARTERIAL HYPERTENSION, III, NOS	1	0	0	0	0
ATHEROSCLEROSIS	0	0	1	0	0
ATHEROSCLEROSIS OF ARTERIES OF THE EXTREMITIES.	1	0	0	0	0
ATHEROSCLEROSIS OF THE CORONARY ARTERIES	1	0	0	0	0
BORDERLINE CARDIOMEGALY	0	1	0	0	0
CORONARY ARTERY DISEASE	0	1	0	0	0
CORONARY HEART DISEASE	1	0	0	0	0
DIFFUSE MODERATE CORONARY DISEASE	0	0	0	1	0
DYASTLIC FUNCTION DISTURBANCE IN THE RIGHT CHAMBER OF THE HEART (STAGE 1).	0	0	1	0	0
EXACERBATION OF HYPERTENSION	1	0	0	0	0
HEART PALPITATION	0	3	0	0	0
HIGH BLOOD PRESSURE	0	1	0	0	0
HYPERTENSION	5	3	1	0	0
HYPERTENSION WORSENING	0	1	0	0	0
HYPERTENSIVE CARDIOVASCULAR DISEASE	0	0	0	0	1
HYPOTENSION	0	0	1	0	0
LEFT ARM HEMATOMA	0	1	0	0	0
MALIGNANT HYPERTENSION	0	1	0	0	0
MYOCARDIAL INFARCTION	1	1	0	0	0
NON-ST ELEVATION MYOCARDIAL INFARCTION	0	0	1	0	0
OCCLUSION AT DISTAL PART OF PERONEA ARTERIA	1	0	0	0	0
OCCLUSION OF THE ARTERIA ILIACA ON THE RIGHT	0	0	1	0	0
PALPITATIONS	0	0	1	0	0
PALPITATIONS (NOT YET DIAGNOSED)	0	0	1	0	0
PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA	0	0	1	0	0
RIGHT FEMORAL ARTERY OCCLUSION	0	0	1	0	0
SINUS BRADYARRHYTHMIA	1	0	0	0	0
TACHYCARDIA	0	1	1	0	0
THROMBOSIS OF SUPERFICIAL VEIN OF LEFT LOWER LIMB	1	0	0	0	0
THROMBOSIS OF THE RIGHT RADIAL VEIN	0	0	0	1	0
UNSTABLE ANGINA	0	0	1	0	0
VARICOSE VEINS OF THE LOWER LIMB	0	1	0	0	0
WORSENING HIGH BLOOD PRESSURE	0	1	0	0	0
WORSENING HYPERTENSION	2	3	0	0	0
WORSENING HYPERTENSION (UNCONTROLLED DRUGS)	0	1	0	0	0
WORSENING OF HYPERTENSION	1	5	0	0	0
WORSENING OF VENTRICULAR TACHYCARDIA	0	1	0	0	0
Total	18	27	12	1	1

Reviewer Analysis, JMP Analysis, adae dataset, Cardiac and Vascular AEs during Treatment Period 1 by Epoch

Table 10 Cardiac and Vascular Adverse Events by Preferred Term in Safety Population During Treatment Period Week 16 to 24

	Week 16 up to Week 24
	EPOCH
	BLINDED TREATMENT
	TRTA
AETERM	**Apremilast 30 mg BID**	**BMS-986165 6 mg QD**
ACCELERATED HYPERTENSION	1	0
AGGRAVATION OF CONCOMITANT ILLUNESS (HYPERTENTION)	1	0
ARTERIAL HYPERTENSION	0	1
ATRIAL FIBRILLATION	0	2
ATRIAL FIBRILLATION RECURRENCE	0	1
BIGEMINIA	0	1
DEGRADATION OF HYPERTENSION	0	1
HYPERTENSION	1	4
INTERMITTENT PALPITATIONS	0	1
LEFT BASILIC VEIN THROMBOSUS-SUPERFICIAL	0	1
ORTHOSTATIC HYPOTENSION	0	1
PREMATURE VENTRICULAR CONTRACTIONS	0	1
SINUS BRADYCARDIA	0	1
SUPRAVENTRICULAR TACHYCARDIA	0	1
TACHYCARDIA	1	0
UNSTABLE ANGINA	0	2
VENTRICULAR EXTRASYSTOLE	0	1
WORSENING HYPERTENSION	1	1
WORSENING OF HYPERTENSION	0	1
WORSENING OF ISCHEMIC HEART DISEASE	0	1
TOTAL	5	22

Reviewer Analysis, JMP Analysis, adae dataset, Cardiac and Vascular AEs during Treatment Period 2 by Epoch

Table 11 Cardiac and Vascular Adverse Events by Preferred Term in Safety Population During Treatment Period Week 24 to 52

	Week 24 up to Week 52					
	EPOCH					
	BLINDED TREATMENT			FOLLOW-UP		
	TRTA			TRTA		
AETERM	**Apremilast 30 mg BID**	**BMS-986165 6 mg QD**	**Placebo**	**Apremilast 30 mg BID**	**BMS-986165 6 mg QD**	**Placebo**
ACUTE PERICARDITIS	0	1	0	0	0	0
AORTOILIAC OCCLUSIVE DISEASE(LERICHEA SYNDROME)	0	1	0	0	0	0
ARTERIAL HYPERTENSION	0	3	1	0	0	0
ATRIAL FIBRILLATION	0	1	0	0	1	0
BENIGN ESSENTIAL HYPERTENSION	1	0	0	0	0	0
DAILY HEART PALPITATIONS	0	1	0	0	0	0
DILATION OF PELVIC VEINS	0	1	0	0	0	0
FEELING COLD OF FINGERS (LOWER EXTREMITIES)	0	1	0	0	0	0
HAEMATOMA ON THE LEFT CALF	0	1	0	0	0	0
HIGH BLOOD PRESSURE	0	1	0	0	0	0
HIPERTENSION	0	1	0	0	0	0
HYPERTENSION	0	10	0	0	0	0
HYPERTENSION EXACERBATION	0	0	0	0	0	1
HYYPERTENSION	1	0	0	0	0	0
INCREASED HYPERTENSION	0	1	0	0	0	0

ISCHEMIC CLOT OF RIGHT LEG	0	1	0	0	0	0
PALPATATIONS	0	1	0	0	0	0
PALPITATIONS	0	1	0	0	0	0
PERICARDIAL EFFUSION	0	0	1	0	0	0
PERICARDITIS RECURRENCE IN THE POST OPERATIVE STATE	0	1	0	0	0	0
PREMATURE VENTRICULAR CONTRACTIONS	0	0	0	0	1	0
PREMATURE VENTRICULAR DEPOLARIZATION	0	1	0	0	0	0
RIGHT BUNDLE BRANCH BLOCK	0	1	0	0	0	0
RUPTURA OF VARICOSE VEIN ON RIGHT LOWER EXTREMITY	0	0	1	0	0	0
SHOCK	0	1	0	0	0	0
SINUS TACHYCARDIA	0	0	0	1	0	0
SUSPECTED ARRHYTHMIA (NOT CONFIRMED)	0	1	0	0	0	0
TYPE A DISSECTION TO AORTIC ROOT	0	1	0	0	0	0
WORSENING HIGH BLOOD PRESSURE	0	0	0	0	1	0
WORSENING HYPERTENSION	0	2	0	0	0	0
WORSENING OF ATHEROSCLEROTIC HEART DISEASE	0	1	0	0	0	0
WORSENING OF HYPERTENSION	1	2	2	0	0	0
TOTAL	3	37	5	1	3	1

Reviewer Analysis, JMP Analysis, adae dataset, Cardiac and Vascular AEs during Treatment Period 3 by Epoch

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/s/

CHARU GANDOTRA
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FORTUNATO F SENATORE
05/31/2022 05:52:29 PM

NORMAN L STOCKBRIDGE
06/01/2022 05:42:35 AM

CONSULTATIVE REVIEW AND EVALUATION OF CLINICAL DATA
CONSULT

Consultant Reviewer:	Roberta Rasetti, MD, PhD, Clinical Reviewer, Division of Psychiatry (DP) Pamela Horn, MD, Clinical Team Leader, DP
Consultation Requestor:	Maryjoy Mejia, MD, Medical Officer, Division of Dermatology and Dentistry (DDD)
Subject of Request:	NDA 214958; Deucravacitinib
Date of Request:	02/14/2022
Date Received:	02/24/2022
Desired Completion Date:	04/18/2022

I. Background

Deucravacitinib (also known as BMS-986165, hereafter referred to as DEUC), a selective tyrosine kinase 2 (TYK2) inhibitor, is under review for the treatment of adults with moderate-to-severe plaque psoriasis. The proposed oral dosing regimen is 6 mg once daily. DEUC is also being developed for the treatment of other immune-mediated diseases such as psoriatic arthritis (PsA), systemic lupus erythematosus (SLE), Crohn's disease (CD), and ulcerative colitis (UC).

Psoriasis and agents to treat psoriasis have been associated with an increased risk of depression, suicidal thoughts and behaviors, and anxiety[1]. The prevalence of comorbid depression in patients with psoriasis is estimated to be between 20% and 30%[2, 3] and psoriasis patients are 1.5 times more likely to show depressive symptoms than individuals without psoriasis[4]. Depression and suicidal thoughts and behaviors are described in the Warnings and Precautions section as adverse reactions associated with Otezla (apremilast), a phosphodiesterase-4 inhibitor approved for the treatment for moderate to severe plaque psoriasis.

II. Specific Consultative Request

Based on the epidemiologic association between psoriasis and depression and suicidal ideation and behavior, and in light of the warning regarding psychiatric adverse reactions associated with apremilast, DDD requested DP's assessment of psychiatric adverse events (AEs), including suicide-related AEs, in the DEUC NDA application.

[1] Liang SE, Cohen JM, Ho RS. Psoriasis and suicidality: a review of the literature. Dermatol Ther 2019;32:e12771
[2] Dowlatshahi EA, Wakkee M, Arends LR, Nijsten T. The prevalence and odds of depressive symptoms and clinical depression in psoriasis patients: A systematic review and meta-analysis. J Invest Dermatol 2014;134:1542-51.
[3] Esposito M, Saraceno R, Giunta A, Maccarone M, Chimenti S. An Italian study on psoriasis and depression. Dermatology 2006;212:123-7.
[4] Hedemann TL, Liu X, Kang CN, Husain MI. Associations between psoriasis and mental illness: an update for clinicians. Gen Hosp Psychiatry. 2022 Mar-Apr;75:30-37. doi: 10.1016/j.genhosppsych.2022.01.006. Epub 2022 Jan 25. PMID: 35101785.

Specifically, DDD asked for responses to the following:

- Is the Applicant's search and analyses adequate for assessing the suicidal ideation and behavior (SIB) safety for this product?

- Please provide your assessment of SIB safety and advise on whether you would recommend labeling or additional data/analysis to better assess/describe SIB safety.

III. Review of Clinical Data

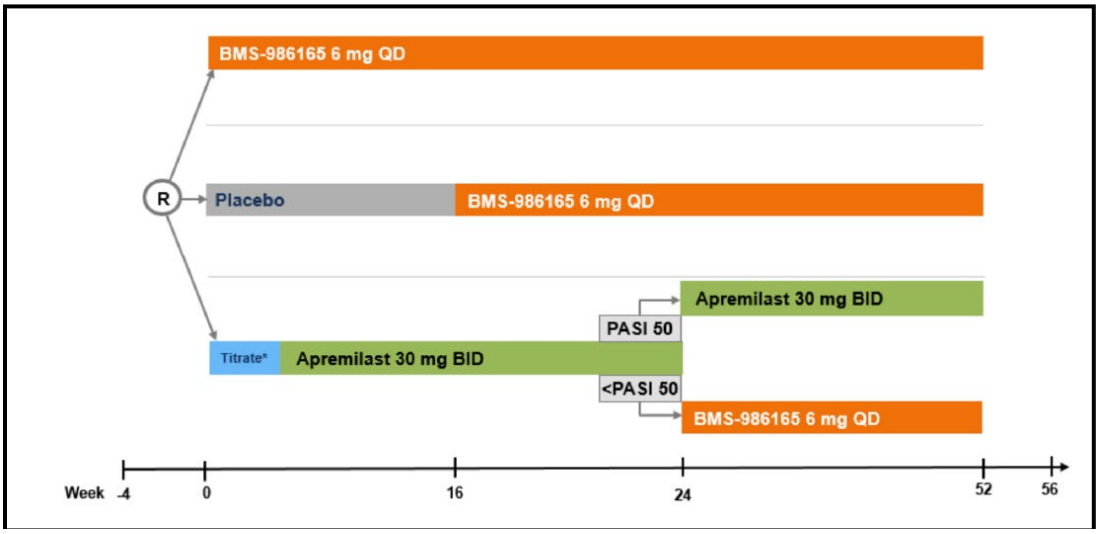
A. Selection of Relevant Clinical Trials

The psychiatric safety analyses mainly focused on the placebo-controlled trials because they provide a direct comparison of the DEUC safety profile with that of a placebo control as well as an active comparator (apremilast). These trials were pooled together in the Controlled Safety Data Pool.

a. Controlled Safety Data Pool

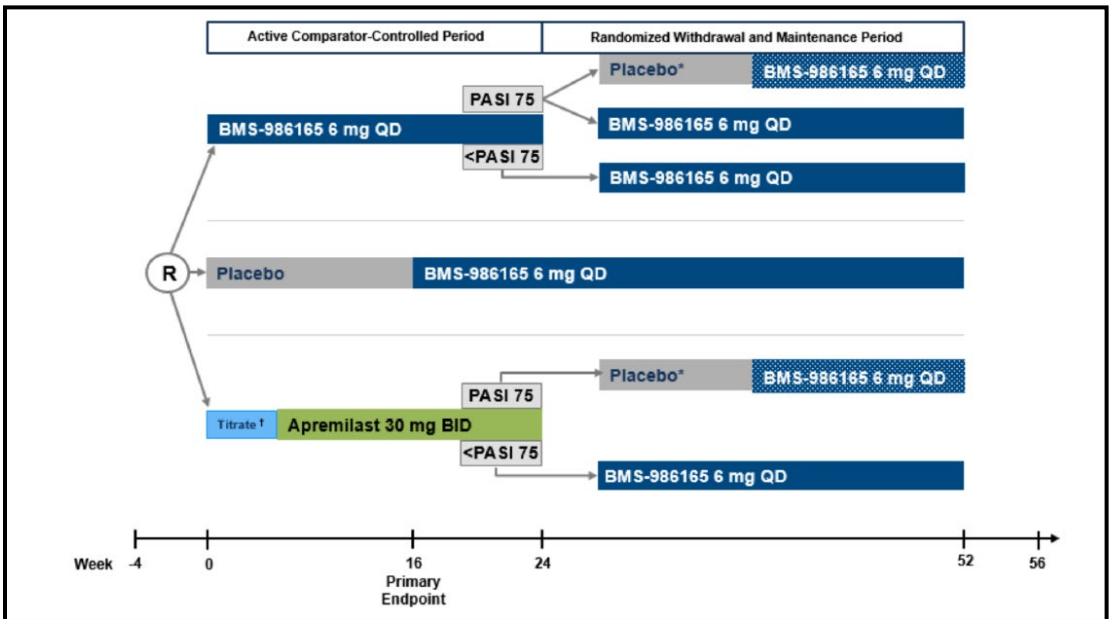
The Controlled Safety Data Pool comprises two pivotal, randomized, placebo- and apremilast-controlled phase 3 studies (IM011046 and IM011047), which had identical eligibility criteria and were of identical study designs until Week 24. In both studies, subjects with moderate-to-severe plaque psoriasis who were candidates for phototherapy or systemic therapy were randomized to receive DEUC 6 mg QD, placebo, or apremilast 30 mg twice daily (approved dose). Study designs for Study IM011046 and Study IM011047 are provided in Figure 1 and Figure 2.

Figure 1. Study Design for Study IM011046



PASI = Psoriasis Area and Severity Index; QD = quaque die (once a day); BID = bis in die (twice a day).
Source: Derived from Applicant's Integrated Statistical Analysis Plan for Safety – Appendix 1.

Figure 2. Study Design for Study IM011047



PASI = Psoriasis Area and Severity Index; QD = quaque die (once a day); BID = bis in die (twice a day).
Source: Derived from Applicant's Integrated Statistical Analysis Plan for Safety – Appendix 1.

Placebo- and apremilast-controlled Period – Week 0 to Week 16

During this period, subjects kept their original randomization to DEUC, apremilast or placebo (before switching of placebo-treated subjects to a DEUC treatment arm at Week 16 and switching or re-randomization at Week 24 in the DEUC or apremilast arms, varying by study). For the placebo-controlled period of the Controlled Safety Data Pool, the pooled treatment arms were DEUC 6 mg QD (n=842), placebo (n=419), or apremilast 30 mg BID (n=422).

Apremilast-Controlled Period – Week 0 to Week 24

In addition to the *Placebo- and apremilast-controlled Period* (0-16 weeks), safety data was summarized with apremilast as a comparator for the period from Week 0 to Week 24 in the Controlled Safety Data Pool (DEUC 6 mg QD (n=842) or apremilast 30 mg BID (n=422)).

DEUC Exposure Period - Week 0 to Week 52

The DEUC Exposure period covers timing from baseline (Week 0) to end of the study (Week 52). This review did not focus on comparisons between DEUC and apremilast arms beyond week 24 because no subjects remained on apremilast beyond Week 24 in Study IM011047, and in Study IM011046 (Figure 1) non-responder subjects (as measured by Psoriasis Area and Severity Index - PASI) originally randomized to apremilast were switched to DEUC treatment at Week 24 rendering the remaining subjects treated with apremilast beyond Week 24 a non-randomized responder subset of the original apremilast arm. Because we cannot exclude a correlation

between risk of psychiatric adverse reactions and response to apremilast treatment, this study design may have introduced unmeasured bias and comparisons between the DEUC arm and the responder subset of the apremilast arm may not be valid. Sixteen to 24 weeks of controlled safety data is typically deemed adequate to assess for treatment-emergent psychiatric adverse reactions and thus this is not a major limitation of the safety data.

b. Non-Pooled Safety Data

The phase 2 study in psoriasis (IM011011), the phase 2 study in PsA (IM011084), and the clinical pharmacology studies are not included in the pooled summaries. Additionally, ongoing regional studies in psoriasis and ongoing studies in other indications (SLE, CD, UC) are not included in the pooled safety analyses. Safety narratives for deaths and psychiatric symptoms were reviewed for these studies.

B. Psychiatric Inclusion/Exclusion Criteria

In the phase 3 studies, subjects were excluded if they had any significant or uncontrolled neuropsychiatric illness or any lifetime history of suicidal ideation, suicidal behavior, or suicide attempts by medical history or by electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) evaluation or were clinically deemed to have an elevated suicide risk by the investigator. These criteria would be expected to reduce the baseline risk of suicidal thoughts and behaviors compared to the target population of patients with moderate to severe plaque psoriasis.
In Study IM011046, 1.6% (15/965) subjects screen-failed because they met the exclusion criteria above. In Study IM011047, 1.4% (21/1519) subjects screen-failed because they met the exclusion criteria above.

C. Psychiatric Safety Monitoring

Because of the epidemiologic association between psoriasis and depression and suicidal ideation and behavior, and in light of the depression warning associated with apremilast, SIB events were adjudicated by experts. The SIB Adjudication Committee, an independent, external, blinded committee of subspecialty experts, adjudicated and confirmed diagnoses of suicidal ideation or behavior, including attempted deaths or self-injury, and all deaths.

Subjects were required to discontinue investigational product (IP) (and non-IP at the discretion of the investigator) if the subject reported suicidal ideation, suicidal behavior, or suicide attempts at any time after randomization, or there was documented suicidal behavior at any time during the study.

In addition to the events that were adjudicated, the studies included regular assessments of depression and suicidality using the following rating scales:

- The 8-item Patient Health Questionnaire (PHQ-8): PHQ-8 is a self-administered diagnostic and severity measure for depressive disorders. The PHQ-8 consists of eight of the nine

criteria (questions) on which the Diagnostic and Statistical Manual of Mental Disorders-IV diagnosis of depressive disorders is based. It is based on a 2-week recall period and scored on a scale of 0 to 3: Not at All (0), Several Days (1), More than Half the Days (2), and Nearly Every Day (3). Scoring interpretation is as follows: 0-4 no significant depressive symptoms (referred to as "none"), 5-9 mild depressive symptoms, 10-14 moderate depressive symptoms, 15-19 moderately severe depressive symptoms, and 20-24 severe depressive symptoms. The PHQ-8 assessments were performed at Screening, Baseline, Week 8, Week 16, Week 28, Week 40, and Week 52.

- The electronic Columbia-Suicide Severity Rating Scale (eC-SSRS): eC-SSRS is a self-administered questionnaire that assesses suicidal ideation and suicidal behavior. Subjects respond to standardized clinical questions that are presented in a uniform fashion. The eC-SSRS defines five subtypes of suicidal ideation and of behavior in addition to self-injurious behavior with no suicidal intent. The eC-SSRS assessments were performed at Screening, Baseline, Week 8, Week 16, Week 28, Week 40, and Week 52.

Although the PHQ-8 scale and the C-SSRS were reasonable instruments to use in the development program, assessments were infrequent. Optimally, assessments should have been conducted every two weeks for the first eight weeks of the study rather than every 8 weeks, but the available data can be used to assess SIB safety.

D. Coding of Psychiatric Adverse Events

The Applicant's coding of investigator adverse event terms to MedDRA preferred terms was evaluated by examination of adverse event datasets for the two phase 3 trials included in the Controlled Safety Data Pool. All events classified under the SOC of Psychiatric Disorders were examined. Negative thoughts and altered mood were not coded under depression by the Applicant and were recoded for this review as depression. In addition, one case of acute drug intoxication of methamphetamine was identified under the SOC of Injury/Poisoning, although not under the SOC of Psychiatric Disorders. Overall, the coding of reported terms to preferred terms was acceptable.

E. Review of Deaths

Overall, 17 deaths were reported in all datasets. Each narrative of death was reviewed, and none was by suicide or related to psychiatric conditions. One placebo-treated patient had a death by car accident in the PsA Study (IM011084), making vehicle suicide a possibility (although very unlikely).

F. Other Non-Fatal Serious Adverse Events

Non-fatal serious adverse events (SAEs) were reviewed for psychiatric serious adverse events.

<u>Controlled Safety Data Pool</u>

Placebo- and apremilast-controlled Period

Analysis of the Adverse-Events Analysis Dataset (AEAD.xpt) revealed one serious adverse event of major depression in the placebo group (subject IM011047-(b) (6)), identified by the Applicant as well. This event was coded as severe and led to treatment discontinuation (refer to paragraph Discontinuation due to AEs).

Apremilast-controlled Period

No SAEs in the SOC of Psychiatric Disorders were identified in the DEUC or apremilast groups in the *Apremilast-controlled Period* using the AEAD dataset.

A review of the SAE narratives identified an SAE in the DEUC arm of psychiatric interest. A 41-year-old male (IM011046-(b) (6)) was hospitalized on Day 8 due to SAE of toxicity to unknown amount of methamphetamine ingestion by the subject, complicated by status epilepticus, that required intubation. The narrative reports that the subject's mental status improved off sedation and the subject was extubated same day (Day 8). On Day 10, toxicity to various agents was resolved. On Day 96 ((b) (6)), the subject withdrew consent from the study, with the last dose received on Day 16 ((b) (6)). There is not enough information to determine if methamphetamine intoxication was intentional or accidental, or if it was for a recreational or self-injurious purpose. Causality with study drug cannot be determined.

Non-Pooled Safety Data

Evaluation of safety narratives in the ongoing phase 3 studies in psoriasis and in the ongoing blinded studies in non-psoriasis indications did not reveal SAEs in the SOC of Psychiatric Disorders.

G. Treatment Discontinuation due to AEs

Controlled Safety Data Pool

Placebo- and apremilast-controlled Period

Table 1 reports discontinuations due to AEs in the SOC of Psychiatric Disorders across the three treatment groups during the *Placebo- and apremilast-controlled Period*. The incidence was similar across groups (0.7% DEUC, 0.9% apremilast, 0.5% placebo), with preferred terms (PT) for psychiatric disorders evenly distributed across groups.

Table 1. Treatment Discontinuation Due to Adverse Events – Placebo- and apremilast-controlled Period (Weeks 0 to 16)

SOC PT	DEUC 6 mg QD N = 842			Apremilast 30 mg BID N=422			Placebo N = 419		
	Events	*Subjects n*	*% (n/N)*	*Events*	*Subjects n*	*% (n/N)*	*Events*	*Subjects n*	*% (n/N)*
Psychiatric Disorders	6	6	0.7	5	4	0.9	2	2	0.5
Anxiety	0	0	0	3	3	0.7	0	0	0
Panic attack	1	1	0.1	0	0	0	0	0	0
Depression	0	0	0	0	0	0	1	1	0.2
Major depression	0	0	0	0	0	0	1	1	0.2
Depressed mood	1	1	0.1	0	0	0	0	0	0
Mood altered	1	1	0.1	0	0	0	0	0	0
Insomnia	2	2	0.2	1	1	0.2	0	0	0
Suicidal ideation/behavior	1	1	0.1	1	1	0.2	0	0	0

QD = quaque die (once a day); BID = bis in die (twice a day).
Source: Clinical Reviewer's Summary based on Subject-Level Analysis Dataset (ADSL.xpt) and Adverse-Event Analysis Dataset (ADAE.xpt) of Integrated Summary of Safety of Controlled Clinical Studies and Single Subject Narratives of Safety of Controlled Clinical Studies.

The analysis grouping together the PTs "Depression," "Major Depression," "Mood altered," and "Depressed mood" did not reveal differences across groups (0.2% DEUC, 0% apremilast, 0.5% placebo).

As reported in Table 1, one subject in the DEUC group and one subject in the apremilast group reported suicidal ideation/behavior (an aborted suicide attempt and suicidal ideation, respectively) resulting in treatment discontinuation. The subject in the DEUC group is subject IM011047-[redacted] (b) (6), who reported "Suicidal Behavior – Aborted Attempts" on the eC-SSRS at Week 12 and treatment was discontinued. This event was not coded as an AE and was not reported in the database of AEs provided by the Applicant. For this reason, Table 1 differs from Table S.5.10 of Summary of Clinical Safety provided by the Applicant.

Apremilast-controlled Period

Compared to Week 0 to 16, there were two more subjects in the DEUC group from week 16 to 24 who discontinued: one due to an AE of depression and one due to an AE of suicidal ideation. In the apremilast group from week 16 to 24, there was one additional subject who discontinued due to an AE of negative thoughts.

Table 2. Treatment Discontinuations Due to Adverse Events – Apremilast-controlled Period (Weeks 0 to 24)

SOC PT	DEUC 6 mg QD N = 842			Apremilast 30 mg BID N=422		
	Events	*Subjects n*	*% (n/N)*	*Events*	*Subjects n*	*% (n/N)*
Psychiatric Disorders	8	7	0.8	6	5	1.2
Anxiety	0	0	0	3	3	0.7
Panic attack	1	1	0.1	0	0	0
Depression	1	1	0.1	0	0	0
Depressed mood	1	1	0.1	0	0	0
Mood altered	1	1	0.1	0	0	0
Negative thoughts	0	0	0	1	1	0.2
Insomnia	2	2	0.2	1	1	0.2
Suicidal ideation	2	2	0.2	1	1	0.2

QD = quaque die (once a day); BID = bis in die (twice a day).
Source: Clinical Reviewer's Summary based on Subject-Level Analysis Dataset (ADSL.xpt) and Adverse-Event Analysis Dataset (ADAE.xpt) of Integrated Summary of Safety of Controlled Clinical Studies and Single Subject Narratives of Safety of Controlled Clinical Studies.

Grouping together the PTs "Depression," "Mood altered," "Depressed mood," and "Negative thoughts," there was an incidence of 0.4 % for DEUC and 0.2% for apremilast.

Table 2 differs from Table S.5.11.4 of Summary of Clinical Safety provided by the Applicant because Table 2 has one more subject with suicidal ideation in the DEUC group, as described in the previous paragraph (*Placebo- and apremilast-controlled Period*).

There was one additional report of suicidal ideation in the DEUC group between Week 16 and Week 24. This subject, IM011047-(b) (6), had onset of depressed mood during the Placebo and apremilast-controlled Period (0-16 Weeks) that persisted into the Apremilast-controlled Period. The same subject also developed suicidal ideation for one day during the Apremilast-controlled Period after Week 16 (0-24 Weeks). This subject was discontinued from the study treatment for depressed mood and suicidal ideation and was counted in both Table 1 and Table 2. Of note, this subject was started on Chantix (varenicline) for smoking cessation 10 days before the onset of suicidal ideation. Chantix is a confounder because it increases the risk of suicidal ideation, among other psychiatric symptoms, as reported in Chantix's label.

Non-Pooled Safety Data

Evaluation of safety narratives in the ongoing phase 3 studies in psoriasis and in the ongoing blinded studies in non-psoriasis indications did not reveal AEs in the Psychiatric Disorders SOC that led to treatment discontinuation.

H. Adverse Events

Controlled Safety Data Pool

Placebo and apremilast-controlled Period

Table 3 reports AEs in the SOC of Psychiatric Disorders across the three treatment groups in the *Placebo and apremilast-controlled Period*.

Table 3. Adverse Events in the SOC of Psychiatric Disorders – Placebo and apremilast-controlled Period (Weeks 0 to 16)

SOC PT	DEUC 6 mg QD N = 842			Apremilast 30 mg BID N = 422			Placebo N = 419		
	Events	*Subjects n*	*% (n/N)*	*Events*	*Subjects n*	*% (n/N)*	*Events*	*Subjects n*	*% (n/N)*
Psychiatric disorders	26	24	2.8	13	12	2.8	12	10	2.4
Depression	5	5	0.6	0	0	0	3	3	0.7
Insomnia	5	5	0.6	4	4	1	2	2	0.5
Depressed mood	4	4	0.5	1	1	0.2	0	0	0
Panic attack	2	2	0.2	0	0	0	0	0	0
Mood altered	2	2	0.2	0	0	0	1	1	0.2
Anxiety disorder	1	1	0.1	0	0	0	1	1	0.2
Anxiety	1	1	0.1	3	3	0.7	1	1	0.2
Distractibility	1	1	0.1	0	0	0	0	0	0
Hallucination	1	1	0.1	0	0	0	0	0	0
Libido decreased	1	1	0.1	0	0	0	1	1	0.2
Abnormal dreams	1	1	0.1	0	0	0	0	0	0
Sleep disorder	1	1	0.1	1	1	0.2	0	0	0
Suicidal ideation/behavior	1	1	0.1	1	1	0.2	0	0	0
Bruxism	0	0	0	1	1	0.2	0	0	0
Major depression	0	0	0	0	0	0	2	1	0.2

Anger	0	0	0	1	1	0.2	0	0	0
Aggression	0	0	0	1	1	0.2	0	0	0
Initial insomnia	0	0	0	0	0	0	1	1	0.2

QD = quaque die (once a day); BID = bis in die (twice a day).
Source: Clinical Reviewer's Summary based on Subject-Level Analysis Dataset (ADSL.xpt) and Adverse-Event Analysis Dataset (ADAE.xpt) of Integrated Summary of Safety of Controlled Clinical Studies and Single Subject Narratives of Safety of Controlled Clinical Studies.

As reported in the discontinuations due to AEs, an AE of suicidal ideation occurred in one subject in the DEUC group and one subject in the apremilast group during the *Placebo and apremilast-controlled Period*. The subject with suicidal ideation in the DEUC group was identified through the eC-RSS score review and not included in the original Applicant's Table 2.7.5.3.-1 of Summary of Clinical Safety, as explained in the previous sections.

Grouping together the PT "Depression," "Major Depression," "Mood altered," "Depressed mood," and "Negative thoughts" in the analysis did not reveal an increased incidence of depressive symptoms in the DEUC group compared to placebo (Table 4). Depressive symptoms occurred in 11 subjects (1.3%) in the DEUC group, in one subject (0.2%) in the apremilast group, and in five subjects (1.2%) in the placebo group. There was a lower incidence in the apremilast group compared to both DEUC and placebo. Table 4 slightly differs from the Applicant's Table 2.7.5.4-1 of Summary of Clinical Safety because the Applicant did not include the PT "Mood altered" (two cases in the DEUC group and one case in the apremilast group).

Table 4. Depressive symptoms – Placebo- and apremilast-controlled Period (Weeks 0 to 16)

Custom Query PT	DEUC 6 mg QD N = 842			Apremilast 30 mg BID N = 422			Placebo N = 419		
	Events	*Subjects n*	*% (n/N)*	*Events*	*Subjects n*	*% (n/N)*	*Events*	*Subjects n*	*% (n/N)*
Depressive symptoms	11	11	1.3	1	1	0.2	6	5	1.2
Depressed mood	4	4	0.5	1	1	0.2	0	0	0
Depression	5	5	0.6	0	0	0	3	3	0.7
Major depression	0	0	0	0	0	0	2	1	0.2
Mood altered	2	2	0.2	0	0	0	1	1	0.2

QD = quaque die (once a day); BID = bis in die (twice a day).
Source: Clinical Reviewer's Summary based on Subject-Level Analysis Dataset (ADSL.xpt) and Adverse-Event Analysis Dataset (ADAE.xpt) of Integrated Summary of Safety of Controlled Clinical Studies using custom query "Depressive symptoms" grouping together PT terms Depressed mood, Depression, Major depression, Mood altered, Negative thoughts.

Among all AEs, two were categorized as severe: one AE of suicidal ideation in the apremilast group and one AE of depressive disorder in the placebo group.

Apremilast-controlled Period – Week 0 to Week 24

Compared to Week 0 to 16, in the DEUC group there were two more subjects with anxiety, one more subject with suicidal ideation, one more subject with depression, one more subject with mood altered, and one more subject with sleep disorder. In the apremilast group, there was one more subject with negative thoughts, and one more subject with insomnia (Table 5).

Table 5. Adverse Events in the SOC of Psychiatric Disorders – Apremilast Controlled Period (Weeks 0 to 24)

SOC PT	DEUC 6 mg QD N = 842			Apremilast 30 mg BID N = 422		
	Events	*Subjects* *n*	*%* *(n/N)*	*Events*	*Subjects* *n*	*%* *(n/N)*
Psychiatric disorders	32	28	3.3	15	14	3.3
Depression	6	6	0.7	0	0	0
Insomnia	5	5	0.6	5	5	1.2
Depressed mood	4	4	0.5	1	1	0.2
Anxiety	3	3	0.4	3	3	0.7
Mood altered	3	3	0.4	0	0	0
Panic attack	2	2	0.2	0	0	0
Sleep disorder	2	2	0.2	1	1	0.2
Suicidal ideation/behavior	2	2	0.1	1	1	0.2
Anxiety disorder	1	1	0.1	0	0	0
Distractibility	1	1	0.1	0	0	0
Hallucination	1	1	0.1	0	0	0
Libido decreased	1	1	0.1	0	0	0
Abnormal dreams	1	1	0.1	0	0	0
Bruxism	0	0	0	1	1	0.2
Negative thoughts	0	0	0	1	1	0.2
Anger	0	0	0	1	1	0.2
Aggression	0	0	0	1	1	0.2

QD = quaque die (once a day); BID = bis in die (twice a day).
Source: Clinical Reviewer's Summary based on Subject-Level Analysis Dataset (ADSL.xpt) and Adverse-Event Analysis Dataset (ADAE.xpt) of Integrated Summary of Safety of Controlled Clinical Studies

As reported in the section "Treatment Discontinuation due to AEs", AEs of suicidal ideation occurred in two subjects in the DEUC group and one subject in the apremilast group during the *Apremilast-controlled Period*.

Grouping together the PTs "Depression," "Major Depression," "Mood altered," "Depressed mood," and "Negative thoughts" resulted in a higher incidence of depressive symptoms in the DEUC group compared to the apremilast group (Table 6). Depressive symptoms occurred in 13 subjects (1.5%) in the DEUC group and in two subjects (0.5%) in the apremilast group. However, even with this additional 8 weeks of data beyond the placebo-controlled 16-week period, the incidence in the DEUC group is similar to the incidence in the placebo group up through Week 16 of the studies.

Table 6. Depressive symptoms - Apremilast Controlled Period (Weeks 0 to 24)

CUSTOM QUERY PT	DEUC 6 mg QD N = 842			Apremilast 30 mg BID N = 422		
	Events	*Subjects* *n*	*%* *(n/N)*	*Events*	*Subjects* *n*	*%* *(n/N)*
Depressive symptoms	13	13	1.5	2	2	0.5
Depression	6	6	0.7	0	0	0
Depressed mood	4	4	0.5	1	1	0.2
Mood altered	3	3	0.4	0	0	0
Negative thoughts	0	0	0	1	1	0.2

QD = quaque die (once a day); BID = bis in die (twice a day).
Source: Clinical Reviewer's Summary based on Subject-Level Analysis Dataset (ADSL.xpt) and Adverse-Event Analysis Dataset (ADAE.xpt) of Integrated Summary of Safety of Controlled Clinical Studies using custom query "Depressive symptoms" grouping together PT terms Depressed mood, Depression, Major depression, Mood altered, Negative thoughts.

There was one severe AE of suicidal ideation in the apremilast group.

I. Psychiatric assessment - Scale Data (eC-SSRS and PHQ-8)

Controlled Safety Data Pool

Placebo- and apremilast-controlled Period

eC-SSRS

The proportion of subjects who had any positive eC-SSRS score at baseline was low (DEUC 0.08%, apremilast 1.2%, placebo 0.05%).

The incidence of subjects who had a positive eC-SSRS score at Week 8 and Week 16 (scheduled visits) remained low and was similar across groups (Table 7). eC-SSRS data were missing in 9% of subjects in the DEUC group, 13% of subjects in the apremilast group, and in 14% of subjects in the placebo group, and incidence is calculated based on the number of subjects who had evaluable eC-SSRS data.

Table 7. eC-SSRS Summary – Subjects with positive eC-SSRS at Week 8 or Week 16

Visit	**Subcategory**	**DEUC 6 mg QD N =842**	**Apremilast 30 mg BID N=422**	**Placebo N = 419**
Weeks 8 and Week 16		N=768 (%)	N=367 (%)	N=359 (%)
	Non-suicidal Self-Injurious Behavior	2 (0.2)	0	0
	Ideation Wish to Be Dead or Not Wake Up	1 (0.1)	3 (0.8)	3 (0.8)
	Ideation Nonspecific Thoughts	1 (0.1)	0	0

	Ideation Specific Thoughts of Method	0	1 (0.3)	0
	Ideation Some Intent to Act, No Plan	0	0	0
	Preparatory Actions	0	0	0
	Aborted Attempts	0	0	0
	Interrupted Attempts	0	0	0
	Actual Attempts	0	1 (0.3)	0
	Complete suicide	0	0	0
Total		6 (0.7)	3 (0.8)	3 (0.8)

QD = quaque die (once a day); BID = bis in die (twice a day).
Self-injurious behavior, suicidal ideation or behavior defined as having one Yes recorded for a subcategory. Only the worst postbaseline score was counted in each subject.
Source: Clinical reviewer's summary using eC-SSRS Analysis Dataset (adecssrs.xpt) submitted in Applicant's response to FDA's Information Request (NDA 214958, SDN 16, April 5, 2022).

Some subjects were evaluated with eC-SSRS outside the scheduled visits at Week 1, Week 4, and Week 12. Table 8 reports the worst post-baseline score between Week 1 to Week 16, including unscheduled visits. The apremilast group had a higher incidence of worst post-baseline eC-SSRS score compared to the DEUC and placebo groups. However, only participants who had AEs (which may have been psychiatric or non-psychiatric) had an unscheduled eC-SSRS assessment and the apremilast group had more unscheduled visits, which may have introduced bias and should be interpreted cautiously.

Table 8. eC-SSRS Worst Post-baseline Result Summary – Week 1 through Week 16

Visit	**Subcategory**	**DEUC 6 mg QD N =842**	**Apremilast 30 mg BID N=422**	**Placebo N = 419**
Weeks 0 to 16		N=768 (%)	N=367 (%)	N=359 (%)
	Non-suicidal Self-Injurious Behavior	3 (0.3)	0	0
	Ideation Wish to Be Dead or Not Wake Up	4 (0.5)	7 (1.9)	3 (0.8)
	Ideation Nonspecific Thoughts	2 (0.2)	5 (1.3)	0
	Ideation Specific Thoughts of Method	0	2 (0.5)	0
	Ideation Some Intent to Act, No Plan	0	2 (0.5)	0
	Preparatory Actions	0	0	0
	Aborted Attempts	1 (0.1)	1 (0.3)	0
	Interrupted Attempts	0	0	0
	Actual Attempts	0	1 (0.3)	0
	Complete suicide	0	0	0
	All suicidal behavior	1 (0.1)	2 (0.5)	0
	All items	10 (1.3)	18 (4.9)	3 (0.8)

QD = quaque die (once a day); BID = bis in die (twice a day).Self-injurious behavior, suicidal ideation or behavior defined as having one Yes recorded for a subcategory. Only the worst postbaseline score was counted in each subject.
Source: Clinical reviewer's summary using eC-SSRS Analysis Dataset (adecssrs.xpt) obtained by Applicant's response to FDA's Information Request (NDA 214958, SDN 16, April 5, 2022).

Per the Applicant's report, all eC-SSRS entries were reviewed by the investigators and, along with medical history, were coded as AEs as deemed medically appropriate by the investigator, and suitable action was taken as necessary (e.g., discontinuation from the study or referral to psychiatric facilities). However, despite the Sponsor reporting one subject (IM011047-(b) (6)

(b) (6)) treated with DEUC who had positive "Suicidal Behavior – Aborted Attempts" at the eC-SSRS at Week 12 who was discontinued from treatment, this subject (and event) was not listed among the subjects with AEs and with treatment discontinuation due to AEs in the Adverse Event Analysis Dataset (AEAD.xpt) provided by the Applicant. This subject was included in the analyses conducted in this review.

Most suicidal ideation events coded in the eC-SSRS as "Ideation – Wish to Be Dead" by subjects, were not coded in the AE database because it was not considered medically appropriate by the investigators. Even including these cases, the frequencies of suicidal ideation events in the DEUC and placebo groups were similar, as shown in the eC-SSRS tables.

PHQ-8

Table 9 reports the incidence of worsening of Total Score in PHQ-8 from Baseline to Week 16. PHQ-8 data were missing in 9% of subjects in the DEUC group, 13% of subjects in the apremilast group, and in 13% of subjects in the placebo group, and incidence is calculated for the subjects with available data.

Table 9. PHQ-8 Total Score Shift From Baseline To Week 16

	DEUC 6 mg QD N=842		Apremilast 30 mg BID N=422		Placebo N=419	
SHIFT Week 16	**N= 770**	**%**	**N= 368**	**%**	**N=363**	**%**
0-4 (NONE) to 5-9 (MILD)	32	4.2	28	7.6	29	8
0-4 (NONE) to 10-14 (MODERATE)	10	1.3	4	1.0	5	1.4
0-4 (NONE) to 15-19 (MODERATELY SEVERE)	3	0.4	0	0	0	0
5-9 (MILD) to 10-14 (MODERATE)	5	0.7	3	0.8	9	2.5
5-9 (MILD) to 15-19 (MODERATELY SEVERE)	1	0.1	0	0	1	0.3
5-9 (MILD) to 20-24 (SEVERE)	0	0	0	0	1	0.3
10-14 (MODERATE) to 15-19 (MODERATELY SEVERE)	2	0.3	0	0	1	0.3
10-14 (MODERATE) to 20-24 (SEVERE)	0	0	1	0.3	0	0
15-19 (MODERATELY SEVERE) to 20-24 (SEVERE)	0	0	0	0	1	0.3
Total	53	6.9	36	9.8	47	12.9

QD = quaque die (once a day); BID = bis in die (twice a day).
Source: Clinical reviewer's summary using PHQ-8 Analysis Dataset (adphq8.xpt) submitted in Applicant's response to FDA's Information Request (NDA 214958, SDN 16, April 5, 2022).

Despite having more subjects without evaluable data, the placebo and apremilast groups had a higher percentage of subjects whose depressive symptoms worsened from Week 0 to Week 16 compared to the DEUC group.

Apremilast-controlled Period – Week 0 to Week 24

No new data on eC-SSRS and PHQ-8 were available for the Apremilast-controlled Period because the protocol schedule did not include psychiatric assessments between Week 16 and Week 24, except for unscheduled visits for a few subjects.

J. Other reports - Day 120 Safety Update Report

The 120-day Safety Update presents additional safety data through the cut-off date of 01-Oct-2021 including only Study IM011075, the open label long-term extension study that enrolled participants who completed treatment in either Study IM011046 or IM011047. There were no AEs of suicidal ideation or behavior and there were no new SAEs or AEs leading to discontinuation in the Psychiatric Disorders SOC.

K. Summary of results

Table 10 Results Summary

SAEs				
Placebo	One case of depression			
DEUC	One case of intoxication with methamphetamine			
Treatment Discontinuation Due to AEs				
Placebo- and apremilast-controlled 0-16 W			Apremilast Controlled 0-24 W	
All psychiatric AEs	DEUC	0.7%	DEUC	0.8%
	Apremilast	0.9%	Apremilast	1.2%
	Placebo	0.5%		
Depression	DEUC	0.2%	DEUC	0.4%
	Apremilast	0%	Apremilast	0.2%
	Placebo	0.5%		
AEs				
Placebo- and apremilast-controlled 0-16 W			Apremilast Controlled 0-24 W	
All psychiatric AEs	DEUC	2.8%	DEUC	3.3%
	Apremilast	2.8%	Apremilast	3.3%
	Placebo	2.4%		
Depression	DEUC	1.3%	DEUC	1.5%
	Apremilast	0.2%	Apremilast	0.5%
	Placebo	1.2%		
Psychiatric Assessment Scales				
Placebo- and apremilast-controlled 0-16 W			Apremilast Controlled 0-24 W	
eC-SSRS worst post-baseline all SB	DEUC	0.1%	N/A	
	Apremilast	0.5%		
	Placebo	0%		

PHQ-8 shift	DEUC Apremilast Placebo	6.9% 9.8% 12.9%	N/A

SAE = Serious Adverse Events; AE = Adverse Events; SB = suicidal behavior; W = Weeks.; N/A = Not Applicable.
Source: Clinical reviewer's summary of data presented in this review.

IV. Conclusions and Recommendations

Generalizability of Study Results to Target Population

Exclusion of subjects with any clinically significant or uncontrolled neuropsychiatric illness or any lifetime history of suicidal ideation or behavior limits the generalizability of the safety findings to the target population. Although excluding patients with unstable neuropsychiatric illness appears justified, exclusion of any clinically significant neuropsychiatric illness could lead to exclusion of a large proportion of eligible participants. In addition, the investigators and Sponsor should avoid exclusion of subjects with any lifetime history of suicidal ideation or behavior a priori, as it is important for these subjects to be studied because they represent a portion of real-world patients with psoriasis. As a general rule, those with recent suicidal behavior (i.e., attempts) within the past month and/or active SIB on screening should be excluded and referred as needed to appropriate psychiatric intervention.

Safety monitoring

The prospective psychiatric safety monitoring during the clinical trials included the PHQ-8 scale and suicidal ideation and behavior monitoring that mapped to the eC-SSRS, which were reasonable instruments to use in the development program. Optimally, assessments should have been conducted every two weeks for the first eight weeks of the study rather than every eight weeks, but the available data can be used to assess SIB safety.

SIB

No subject died due to suicide during the developmental program of DEUC. During the placebo- and apremilast-controlled period (from 0 to 16 weeks), the only actual attempt was reported in a subject receiving apremilast (Table 10). A case of "Suicide Behavior - Aborted Suicide", identified by the eC-SSRS, in a subject in the DEUC treatment group, led to DEUC treatment discontinuation at Week 12, but was not listed as an AE by the Applicant. Considering this last event as a possible instance of suicidal behavior, 0.1% of subjects receiving DEUC had suicidal behavior, compared to 0% in subjects receiving placebo, and 0.2% of subjects receiving apremilast. There was one subject treated with DEUC that experienced overdose with psychostimulants requiring intubation, as reported in the safety narratives, but the intent of the overdose, intentional vs. accidental and recreational use vs. self-injurious behavior, could not be determined based on the limited information provided in the Clinical Safety Report.

If the analyses are extended to Week 24 (apremilast controlled period), one additional subject in the DEUC group reported suicidal ideation from Week 16 to Week 24 compared to zero subjects in the apremilast group, for a total of 0.2% in the DEUC group (2/842) vs. 0.2% in the apremilast group (1/422) in the 0 to 24 Week period. Of note, this subject started Chantix, known to be associated with psychiatric disorders including suicidal ideation, ten days prior to having suicidal ideation.

In summary, there does not appear to be a signal for suicidal ideation or behavior in the *Controlled Safety Data Pool.* However, the generalizability of this finding is limited by the overall rare incidence of SIB events and the selection of the treatment population. Indeed, the treatment population was selected excluding subjects with any clinically significant uncontrolled neuropsychiatric illness or any lifetime history of suicidal ideation or behavior, which is too restrictive. For those subjects with a history of suicidal ideation or behavior, investigators and sponsors should usually consider that exclusion determination on a case-by-case risk-benefit basis for each protocol. Sponsors should avoid exclusion of subjects with any lifetime history of suicidal ideation or behavior a priori, as it is important for these subjects to be studied because they represent a portion of real-world patients with psoriasis, which is the target population. As a general rule, those with recent suicidal behavior (i.e., attempts) within the past month and/or active SIB on screening should be excluded and referred as needed to appropriate psychiatric intervention.

Depressive symptoms

During the placebo- and apremilast-controlled period (from 0 to 16 weeks), 1.3% of subjects treated with DEUC reported depression compared to 1.2% treated with placebo and 0.2% treated with apremilast. A total of 0.2% of subjects treated with DEUC discontinued treatment due to depressive symptoms, compared to 0.5% in placebo-treated subjects and 0% in apremilast-treated subjects. Depression was reported as serious in 0.2% of subjects exposed to placebo, compared to none in DEUC treated subjects. During the 0 to 24 week apremilast-controlled period, 1.5% of subjects treated with DEUC reported depressive symptoms compared to 0.5% treated with apremilast. A total of 0.4% of participants in the DEUC group and 0.2% in the apremilast group discontinued treatment due to depressive symptoms. See summarized findings in Table 10.

Overall, the rate of psychiatric AEs was low in the DEUC group, as well as in the apremilast and placebo groups. There was a slightly higher crude rate incidence of depressive symptoms in the DEUC group compared to the apremilast group in the Apremilast-controlled Period, but the rate in the DEUC group was similar to the rate observed in the placebo group during the Placebo- and apremilast-controlled Period, and does not raise particular concerns at this time.

Recommendations:

1. The psychiatric safety monitoring for the developmental program of DEUC, while not optimal, appeared adequate overall for assessing SIB.

2. Based on the available clinical trial data, there is insufficient evidence of increased risk of suicidal ideation and behavior or other psychiatric adverse reactions with DEUC compared to placebo to recommend specific psychiatric warning language. In addition, the incidence of SIB and depressive symptoms was low and similar across treatment groups and does not appear to meet the typical standard for inclusion in the adverse reactions section of the prescribing information.

3. Although the enrollment criteria appeared to be unnecessarily restrictive with respect to neuropsychiatric illness, very few potential subjects were reportedly excluded from study participation based on these criteria, which somewhat allays concerns that the results could have been made significantly more generalizable to the target population by optimizing enrollment criteria. An additional dedicated safety study that optimizes the study population and safety monitoring for evaluating SIB safety does not appear to be warranted.

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/s/

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Division of Pediatric and Maternal Health Review

Date: April 22, 2022 **Date consulted:** October 14, 2021

From: Jean Limpert, MD, Medical Officer, Maternal Health Team (MHT)
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, MHT, DPMH

Lynne P. Yao, MD, OND, Division Director, DPMH

To: Division of Dermatology and Dentistry (DDD)

Drug: deucravacitinib tablets

NDA: 214958

Applicant: Bristol Myers Squibb Company

Subject: Pregnancy and Lactation Labeling

Indication: For the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy

Materials Reviewed:

- DPMH consult request dated October 14, 2021, DARRTS Reference ID 4872185
- Applicant's submitted background package and proposed labeling for NDA 214958
- Applicant's Information Request (IR) response for NDA 214958 dated March 22, 2022

Consult Question: "DDD requests DPMH's assistance with review of the data for the proposed labeling and asks the division to provide recommendations for sections 8.1 Pregnancy and 8.2 Lactation."

INTRODUCTION AND BACKGROUND

On September 10, 2021, Bristol Myers Squibb Company submitted an original 505(b)(1) NDA for deucravacitinib which is a new molecular entity. The proposed indication is for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. On October 14, 2021, DDD consulted DPMH to assist with the Pregnancy and Lactation subsections of labeling.

Regulatory History

- Deucravacitinib is a novel oral selective inhibitor of Tyrosine kinase 2 (TYK2). Deucravacitinib is not approved in the United States or internationally. There are no approved TYK2 inhibitors.
- Deucravacitinib is in development for use in other immune-mediated diseases, including Phase 2 studies for systemic lupus erythematosus (SLE), Crohn's disease (CD), and ulcerative colitis (UC).
- On March 11, 2022, the Agency sent the applicant an IR for an updated review and summary of pregnancy cases with reported exposure to deucravacitinib during clinical trials. On March 22, 2022, the applicant submitted their response.

Drug Characteristics[1]

- *Drug class*: TYK2 inhibitor
- *Mechanism of Action*: Deucravacitinib is a TYK2 enzyme inhibitor, which belongs to the Janus kinase (JAK) family. Deucravacitinib binds to the regulatory domain of TYK2, stabilizing an inhibitory interaction between the regulatory and the catalytic domains of the enzyme. This results in allosteric inhibition of receptor-mediated activation of TYK2 and its downstream activation of Signal Transducers and Activators of Transcription (STATs) as shown in cell-based assays. JAK kinases, including TYK2, function as pairs of homo- or heterodimers in the JAK-STAT pathways. TYK2 pairs with JAK1 to mediate multiple cytokine pathways and also pairs with JAK2 to transmit signals. The precise mechanism linking inhibition of TYK2 enzyme to therapeutic effectiveness is not currently known.
- *Molecular weight*: 425 Daltons
- *Terminal half-life*: 10 hours
- *Plasma protein binding*: ~ 90%
- *Bioavailability*: 99%
- *Dosing*: 6 mg tablet orally once daily (chronic administration)

Reviewer comment: DPMH reached out to the review team regarding deucravacitinib in comparison to other JAK inhibitors. While deucravacitinib is purported to have a more selective mechanism of action, the similarities and differences from a clinical safety standpoint are still under review.

[1] Draft PI for NDA 214958 with edits from review team as of March 24, 2022

REVIEW
PREGNANCY
Psoriasis and Pregnancy

- The prevalence of psoriasis in females of reproductive potential is approximately 1% and the peak incidence occurs between the age of 30 to 40 years. Plaque psoriasis is the most common form of psoriasis. Disease activity during pregnancy is unpredictable.[2]
- Some studies have suggested that psoriasis increases the risk of gestational diabetes, miscarriage, preeclampsia, and low birth weight but results have been inconsistent and controlled studies have not been conducted.[3,4] Such complications are thought to result from elevated levels of pro-inflammatory cytokines including IL-1, IL-6, and TNF-alpha.[5]
- For pregnant patients with psoriasis involving limited areas of skin, treatment includes topical emollients and topical corticosteroids. Ultraviolet B (UVB) phototherapy is used for more extensive disease and is considered a safe and effective treatment option during pregnancy.[6] Systemic therapies that may be used during pregnancy for severe disease include anti-tumor necrosis factor (TNF) biologics and cyclosporine. Methotrexate and acitretin are psoriasis treatments in nonpregnant patients but are contraindicated during pregnancy because they are teratogenic.
- The Joint American Academy of Dermatology (AAD) and National Psoriasis Foundation (NPF) Guidelines of Care for the Management and Treatment of Psoriasis with Biologics consider anti-TNF biologics safe to use during pregnancy, but infants exposed in utero are considered immunosuppressed up to three months postpartum.[7] The Joint AAD and NPF Guidelines of Care for the Management and Treatment of Psoriasis with Systemic Nonbiologic Therapies notes that pregnancy data for cyclosporine is primarily in organ transplant recipients who typically have numerous comorbidities and multiple concomitant medications. Cyclosporine does not appear to be teratogenic but prematurity and lower birth weights have been reported.[8]

[2] Simionescu, Anca Angela, Bianca Mihaela Danciu, and Ana Maria Alexandra Stanescu. "State-of-the-Art Review of Pregnancy-Related Psoriasis." *Medicina.* 57, no. 8 (2021).
[3] https://mothertobaby.org/fact-sheets/psoriasis-and-pregnancy/, accessed 3/24/22.
[4] https://www.uptodate.com/contents/management-of-psoriasis-in-pregnancy?search=psoriasis%20pregnacny&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1
[5] Simionescu, Anca Angela, Bianca Mihaela Danciu, and Ana Maria Alexandra Stanescu. "State-of-the-Art Review of Pregnancy-Related Psoriasis." *Medicina.* 57, no. 8 (2021).
[6] https://www.uptodate.com/contents/management-of-psoriasis-in-pregnancy?search=psoriasis%20pregnacny&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H10
[7] Menter A, et al. Joint AAD-NPF Guidelines of Care for the Management and Treatment of Psoriasis with Biologics. J Am Acad Dermatol, Volume 80, Number 4: 1029-1072. April 2019.
[8] Menter A, Gelfand JM, Connor C, et al. Joint American Academy of Dermatology-National Psoriasis Foundation guidelines of care for the management of psoriasis with systemic nonbiologic therapies. J Am Acad Dermatol. 2020 Jun;82(6):1445-1486.

Nonclinical Experience

Deucravacitinib was administered orally during the period of organogenesis at doses of 5, 15, or 75 mg/kg/day in rats and 1, 3, or 10 mg/kg/day in rabbits. Deucravacitinib was not associated with embryofetal lethality or fetal malformations in rats or rabbits at 266 times or 91 times the maximum recommended human dose (MRHD) respectively.

In a pre- and post-natal development study in rats, deucravacitinib was administered orally from gestation day 6 through lactation day 20, at doses of 5, 15, or 50 mg/kg/day. At 50 mg/kg/day (110 times the MRHD), F1 offspring had reduced body weight gain during the pre-weaning period. After weaning, body weights of affected F1 offspring gradually normalized to control levels. No maternal effects were observed at 110 times the MRHD. No effects on postnatal developmental, neurobehavioral, or reproductive performance of offspring were observed at 15 mg/kg/day 19 times the MRHD.

For full details, the reader is referred to the Pharmacology/Toxicology review by Yongcheng Huang, PhD.

Clinical Trials

Pregnant females were excluded from clinical trials and females of reproductive potential were required to use contraception while in the study. All female subjects promptly discontinued the study medication at the time of discovery of a positive pregnancy test. The applicant identified 24 pregnancies (13 maternal exposures and 11 paternal exposures) across clinical trials for all indications. Exposures occurred before conception and/or in the first trimester. A tabular summary of pregnancy outcomes for maternal exposures may be found in the applicant's March 22, 2022, IR response (see pages 4 to 8). Among cases reported for paternal exposures, there were 7 live births, 1 elective termination, and 3 unknown outcomes.

Reviewer comment: While the applicant provided pregnancy outcome information for cases with reported paternal exposure, deucravacitinib is not considered genotoxic and paternal exposure would not be expected to impact pregnancy outcomes. Additional details about the cases involving paternal exposure are not discussed further.

Pregnancy Outcomes for Maternal Exposure (n=13):

- 3 live births (all reported as full-term infants; two cases reported first trimester exposure; one case reported pregnancy 14-16 days after last dose of deucravacitinib)
- 4 elective terminations (first trimester exposure in all cases; unwanted pregnancy in one case; reasons not provided for other cases)
- 2 spontaneous abortions (first trimester exposure in one case; unclear timing in second case)
- 1 ectopic pregnancy (first trimester exposure)
- 2 ongoing cases (one case still blinded to study drug)
- 1 unknown outcome (exposure before conception; pregnancy reported "within a few weeks after completing the study")

No congenital malformations were reported. No perinatal complications were reported. The applicant concluded, "The available clinical data on pregnancies reported after exposure to deucravacitinib are limited, but do not suggest a specific safety concern."[9]

Reviewer comment: This reviewer agrees with the applicant's conclusion. The available data are limited to less than fifteen exposures which include peri-conception or first trimester exposure. In each case, deucravacitinib was discontinued once the pregnancy was identified. There are no available data regarding chronic use of deucravacitinib throughout pregnancy.

Review of Literature

Applicant's Review of Literature

The applicant conducted a literature search for publications relevant to pregnancy and deucravacitinib or tyrosine kinase 2 inhibitors. No relevant publications were identified.

DPMH Review of Literature

DPMH performed a search in PubMed, Embase, Micromedex,[10] TERIS,[11] REPROTOX,[12] and *Drugs in Pregnancy and Lactation* [13] to find relevant articles related to the use of deucravacitinib during pregnancy Search terms included "deucravacitinib" AND "pregnancy," "pregnant women," "birth defects," "congenital malformations," "stillbirth," "spontaneous abortion," "miscarriage," and "fetal loss." No relevant information was identified.

Postmarketing Studies

In addition to pharmacovigilance, the applicant plans to conduct a pregnancy surveillance study using United States electronic medical record claims data to examine pregnancy and infant outcomes in women with psoriasis who were exposed to deucravacitinib during pregnancy in the post-marketing setting.[14]

LACTATION

Nonclinical Experience

In animal lactation studies, deucravacitinib was present in rat milk.

For full details, the reader is referred to the Pharmacology/Toxicology review by Yongcheng Huang, PhD.

Review of Pharmacovigilance Database

The applicant did not identify reports relevant to breastfeeding in their pharmacovigilance database.

Review of Literature

Applicant's Review of Literature

[9] Applicant's March 22, 2022 IR response, page 16-17.
[10] https://www.micromedexsolutions.com, accessed 3/3/22.
[11] Truven Health Analytics information. TERIS, accessed 3/3/22.
[12] Truven Health Analytics information. REPROTOX, accessed 3/3/22.
[13] Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 12th edition. 2022, Philadelphia, PA. online, accessed 3/3/22.
[14] Applicant's March 24, 2022, IR response for NDA 214958

The applicant conducted a literature search for publications relevant to lactation and deucravacitinib or tyrosine kinase 2 inhibitors. No relevant publications were identified.

DPMH Review of Literature
This Reviewer performed a search in PubMed, Embase, Micromedex,[15] TERIS,[16] REPROTOX,[17] *Drugs in Pregnancy and Lactation*,[18] *Medications and Mothers' Milk*,[19] and LactMed[20] to find relevant articles related to the use of deucravacitinib during lactation. Search terms included "deucravacitinib" AND "breastfeeding" or "lactation." No relevant information was identified.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL
Nonclinical Experience
Deucravacitinib and its two major human metabolites, BMT-158170 and BMT-153261, tested negative in a battery of genotoxicity studies, i.e., Ames tests (deucravacitinib and metabolites), an in vitro mammalian chromosome aberration test (deucravacitinib), in vitro micronucleus tests (metabolites), and an in vivo mammalian (rat) erythrocyte micronucleus test.[21]

In male rats, deucravacitinib had no effects on reproductive parameters (mating, fertility, and sperm morphology) or early embryonic development of their offspring at oral doses up to 50 mg/kg/day and exposure approximately 247 times the MRHD.

In female rats, deucravacitinib had no effects on mating, fertility, or early embryonic parameters at oral doses up to 50 mg/kg/day and exposure approximately 171 times the MRHD.

For full details, the reader is referred to the Pharmacology/Toxicology review by Yongcheng Huang, PhD.

Review of Pharmacovigilance Database
The applicant did not identify reports relevant to fertility in their pharmacovigilance database.

Review of Literature
Applicant's Review of Literature
The applicant conducted a literature search for publications relevant to fertility and deucravacitinib or tyrosine kinase 2 inhibitors. No relevant publications were identified.

DPMH Review of Literature
This Reviewer performed a search in PubMed and Embase to find relevant articles

[15] https://www.micromedexsolutions.com, accessed 3/3/22.
[16] Truven Health Analytics information. Teris, accessed 3/3/22.
[17] Truven Health Analytics information. Reprotox, accessed 3/3/22.
[18] Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 12th edition. 2022, Philadelphia, PA. online, accessed 3/3/22.
[19] https://www.halesmeds.com, accessed 3/4/22.
[20] https://www.ncbi.nlm.nih.gov/books/NBK501922/, 3/4/22.
[21] Nonclinical Midcycle Review for NDA 214598, Yongcheng Huang, PhD

related to the use of deucravacitinib and effects on fertility. Search terms included "deucravacitinib" AND "fertility," "infertility," "contraception," and "oral contraceptives." No relevant articles were identified.

DISCUSSION AND CONCLUSIONS

Pregnancy

Pregnant females were excluded from clinical trials with deucravacitinib. The 13 reported cases of inadvertent exposure to deucravacitinib during pregnancy are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. There are no data on chronic use of deucravacitinib during pregnancy. There is no published literature regarding deucravacitinib use during pregnancy. The embryofetal and pre- and postnatal studies in animals are reassuring as adverse effects were not observed at clinically relevant exposures.

Psoriasis occurs in 1% of female of reproductive potential, and therefore exposures, both intended and unintended, to deucravacitinib during pregnancy are anticipated. The applicant proposes to perform a medical record claims database study to evaluate the safety of deucravacitinib exposure during pregnancy. DPMH agrees with a claims database study as a complementary study but also recommends a pregnancy exposure registry to evaluate the safety of deucravacitinib during pregnancy. DPMH recommends both safety studies are issued as postmarketing (PMR) requirements. See below for suggested PMR language.

Lactation

Lactating females were excluded from clinical trials with deucravacitinib and no cases relevant to lactation were reported in the clinical trials. There are no published data regarding the presence of deucravacitinib in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Deucravacitinib is transferred into the milk of lactating rats. While deucravacitinib appears to have a unique toxicity profile, it also belongs to the JAK family. While the safety evaluation is still under review, as of April 22, 2022, the review team plans to add Warnings and Precautions for infections, hypersensitivity reactions, lymphoma, and laboratory abnormalities, including creatinine phosphokinase elevations, and liver enzyme elevations. In light of the serious adverse reactions observed for deucravacitinib and for consistency with labeling for other JAK inhibitors, DPMH recommends that labeling state that breastfeeding is not recommended.

Based on the lack of available clinical data and the anticipated use of deucravacitinib in females of reproductive potential, which includes lactating females, DPMH recommends issuing a PMR for a clinical lactation study (milk only) to assess the concentration of deucravacitinib in human milk. See below for suggested PMR language.

Females and Males of Reproductive Potential

There are no clinical data regarding fertility in females and males of reproductive potential. Deucravacitinib was not mutagenic in nonclinical studies. No adverse effects on fertility were observed in animal reproductive studies. DPMH recommends omitting subsection 8.3 in labeling.

PMR RECOMMENDATIONS

DPMH recommends the following:

1. The applicant should conduct a pregnancy exposure registry. The following PMR language is suggested:

   > A prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to TRADENAME during pregnancy to an unexposed control population. The registry should be designed to detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

2. DPMH agrees with the applicant's plan for a claims based study. The following PMR language is suggested:

   > An additional pregnancy study that uses a different design from the pregnancy registry (for example a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to TRADENAME during pregnancy compared to an unexposed control population.

3. The applicant should conduct a milk only lactation study using a validated assay in order to inform the lactation subsection of labeling. The following PMR language is suggested.

   > Perform a lactation study (milk only) in lactating women who have received TRADENAME to assess concentrations of deucravacitinib in breastmilk using a validated assay.

LABELING RECOMMENDATIONS

DPMH revised Highlights, subsections 8.1, 8.2, and section 17 of the draft deucravacitinib labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with the Division on April 22, 2022. DPMH recommendations are below and reflect the discussions with DDD. DPMH refers to the final NDA action for final labeling.

(b) (4)

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

JEAN L LIMPERT
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04/22/2022 10:46:58 AM

LYNNE P YAO
04/22/2022 10:53:56 AM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA-214958
Submission Number	001
Submission Date	9/10/2021
Date Consult Received	10/22/2021
Drug Name	Deucravacitinib
Indication	Moderate-to-Severe Plaque Psoriasis
Therapeutic Dose	6 mg, once daily
Clinical Division	DDD
Protocol Review	link

Note: Any text in the review with a light background should be considered to be copied from the sponsor's document.

This review responds to your consult dated 10/22/2021 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review of protocol dated 07/02/2018 in DARRTS (link);
- Sponsor's clinical study report # IM011048 (SN0001; link);
- Sponsor's proposed product label (SN0001; link); and
- Highlights of clinical pharmacology and cardiac safety (SN0003; link).

1 SUMMARY

No significant QTcF prolongation effect of deucravacitinib was detected in this QT assessment.

The thorough QT study (Study IM011048) was a double-blind, randomized, single-dose (12 mg and 36 mg), placebo- and positive-controlled, crossover study conducted in healthy subjects. Assay sensitivity was established using moxifloxacin (Section 4.5.1). The highest dose evaluated was 36 mg, which covers the high clinical exposure scenario (hepatic impairment, Section 3.1). Data were analyzed using exposure-response analysis as the primary analysis, which did not suggest that deucravacitinib is associated with significant QTc prolonging effect (refer to Section 4.5) – see Table 1 for overall results.

Table 1: Point Estimates and the 90% CIs (FDA Analysis)

ECG Parameter	Treatment	Concentration (ng/mL)	ΔΔQTcF (msec)	90% CI (msec)
QTc	Deucravacitinib 36 mg	315	2.3	(1.4 to 3.2)

For further details of the FDA analysis, please see Section 4.

These findings are further supported by the available nonclinical data (Section 3.1.2), by-time analysis (Section 4.3) and categorical analysis (Section 4.4).

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to SDN001 (link) from the CSS-IRT. Our changes are highlighted (*addition*, ~~*deletion*~~). Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics Cardiac Electrophysiology *At a dose 6 (b) (4) times the (b) (4) recommended dose ~~of the 6 mg once daily~~ (b) (4) ~~in psoriasis patients~~, (b) (4) TRADENAME> does not prolong the QTc interval to any clinically relevant extent.*
We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

Bristol-Myers Squibb is developing deucravacitinib for the treatment of moderate to severe plaque psoriasis (in adults who are candidates for systemic therapy or phototherapy). Deucravacitinib (BMS-986165, DEUC; MW: 425.5) is a tyrosine kinase 2 inhibitor.

The product is formulated as immediate-release film-coated tablet formulation containing 6 mg deucravacitinib for oral administration. The maximum proposed therapeutic dose for the present indication is 6 mg once daily (Study # IM011046 & IM011047). The peak concentrations of 45 ng/mL (Tmax: ~3 h; half-life: ~10 h) are expected at steady state with the proposed therapeutic dose. No significant accumulation is expected at steady state with the proposed maximum therapeutic dose (6 mg once daily; Cmax Racc: ~1.24). The maximum studied dose is 40 mg as a single dose (Cmax: ~410 ng/mL in healthy subjects).

Studies indicate that deucravacitinib primarily eliminated by metabolism (59% of the dose) forming multiple metabolites (M13, BMT-153261 by CYP1A2; M7, BMT-158170 by CES2, and minor M6, BMT-334616 by UGT1A9). The human mass balance study indicates that 13% of the administered dose (as unchanged) is excreted in urine (Study #

IM011016). Increased exposures of deucravacitinib (unbound Cmax: 1.62-fold) were observed in subjects with severe hepatic impairment (Study # IM011062). Deucravacitinib is not recommended in patients with severe hepatic impairment (Child-Pugh C).

The sponsor conducted a thorough QT study to characterize the risk of QT prolongation of deucravacitinib. Refer to previous IRT review dated 07/02/2018 in DARRTS (link). Subjects received a single oral dose of either placebo, 12 mg deucravacitinib, 36 mg deucravacitinib, or moxifloxacin 400 mg on Days 1, 6, 11, and 16. PK samples for analysis of deucravacitinib and its metabolites (BMT-153261 and BMT-158170) were collected. The peak concentration (Cmax: ~315 ng/mL) observed with highest dose studied (i.e., 36 mg single dose) offers ~7-fold margin over the therapeutic exposures (Cmax: ~45 ng/mL) associated with the maximum proposed dose at the steady state. The sponsor highlights that deucravacitinib exhibits a dose proportional increase in exposure (Cmax and AUC) over a dose range of 3 mg to 36 mg.

3.1.2 Nonclinical Safety Pharmacology Assessments

Refer to the sponsor's highlights of clinical pharmacology and clinical safety. The expected peak concentrations of ~45 ng/mL (Free: 19 nM; PPB: ~82%) at steady-state with once daily dosing of 6 mg offers >225-fold margin (hERG – 43.9% inhibition at 4.3 μM). Refer to previous IRT review dated 07/02/2018 in DARRTS (link).

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

The primary analysis for BMS-986165 was based on exposure-response analysis, please see Section 3.2.3 for additional details. In the sponsor's by-time analysis, the largest upper confidence interval bound ΔΔQTcF was below10 msec for both 12 mg and 36 mg BMS-986165.

Reviewer's comment: *Results from FDA reviewer's analysis are similar to sponsor's results. Please see Section 4.3 for additional details.*

3.2.1.1 Assay Sensitivity

Assay sensitivity was established using moxifloxacin.

Reviewer's comment: *The results of the sponsor's analysis show that the study demonstrated assay sensitivity (lower bound at the geometric mean Cmax is >5 msec). Please see Section 4.5.1 for additional details.*

3.2.1.1.1 QT Bias Assessment

Not applicable.

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., >500 msec or >60 msec over baseline), HR (<50 or >100 beats/min), PR (>200 msec and 25% over baseline), and QRS (>120 msec and 25% over baseline).

Reviewer's comment: *FDA reviewer's analysis also shows no significant outliers for any of the ECG intervals.*

3.2.3 Exposure-Response Analysis

The sponsor performed PK/PD analysis to explore the relationship between concentration of deucravacitinib (and its major metabolites BMT-153261, and BMT-158170) and ΔQTcF (change from baseline in QTcF) using a linear mixed-effects approach. The sponsor's final model included the parent analyte only.

The sponsor analysis indicates a concentration dependent increase in QTcF with a slight positive slope of 0.0059 msec/ng/mL (90% CI: 0.0021 to 0.0098 msec/ng/mL). The model predicted ΔΔQTcF (upper confidence interval) values of 2.1 (3.19) msec at the mean peak concentrations for the highest dose studied (i.e., 36 mg, single oral administration: geomean Cmax ~315 ng/mL). Similarly, the model predicted ΔΔQTcF (upper confidence interval) values of 0.7 (1.68) msec at the mean peak concentrations for 12 mg (geomean Cmax ~92 ng/mL) following single oral administration. The results of the sponsor's analysis suggest an absence of significant QTc prolongation at the proposed therapeutic dose (i.e., 6 mg once daily).

Reviewer's comment: *Although there are numerical differences, the results of the reviewer's analysis agreed with the sponsor's conclusion. Please see Section 4.5 for additional details.*

3.2.4 Safety Analysis

Safety population consisted of 40 subjects.

No deaths occurred. Four treatment-emergent SAEs including pharyngitis, trismus, cellulitis, and lymphadenopathy were reported in 1 subject four days after administration of BMS-986165 12 mg. One subject discontinued study drug following administration of moxifloxacin because of elevated blood CPK.

No treatment-emergent cardiac adverse events were reported.

Reviewer's comment: *None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., syncope, significant ventricular arrhythmias, or sudden cardiac death) occurred in this study.*

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., |mean| <10 beats/min) were observed (Section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall, ECG acquisition and interpretation in this study appear acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 By-Time Analysis

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG. The statistical reviewer used a linear mixed model to analyze the drug effect by-time for each biomarker (e.g., ΔQTcF, ΔHR) independently. The default model includes treatment, sequence, period, time (as a categorical variable), and treatment-by-time interaction as fixed effects, and baseline as a covariate. The default model also includes subject as a random effect and an unstructured covariance matrix to explain the associations among repeated measures within the period.

4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTcF for different treatment groups. The maximum ΔΔQTcF values by treatment are shown in Table 2.

Figure 1: Mean and 90% CI of ΔΔQTcF Time-course (unadjusted CIs).

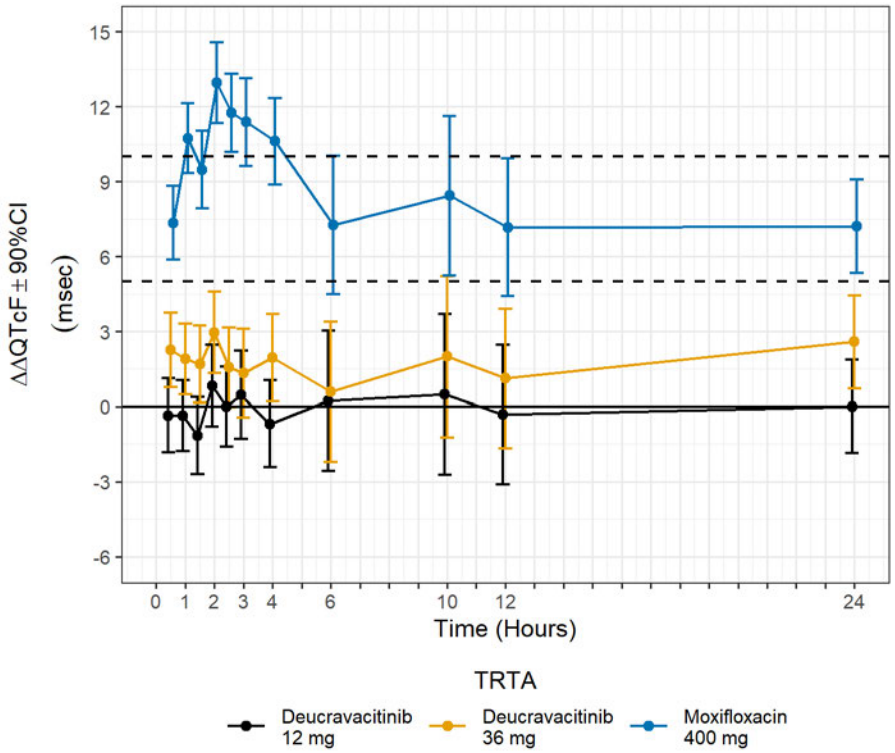


Table 2: Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔQTcF

Actual Treatment	Nact / Npbo	Time (Hours)	ΔΔQTcF (msec)	90.0% CI (msec)
Deucravacitinib 12 mg	39 / 39	10.0	0.5	(-2.7 to 3.7)
Deucravacitinib 36 mg	39 / 39	10.0	2.0	(-1.2 to 5.2)

4.3.1.1 Assay Sensitivity

The primary method for establishing assay sensitivity for this study was based on exposure-response analysis—see Section 4.5.1 for details.

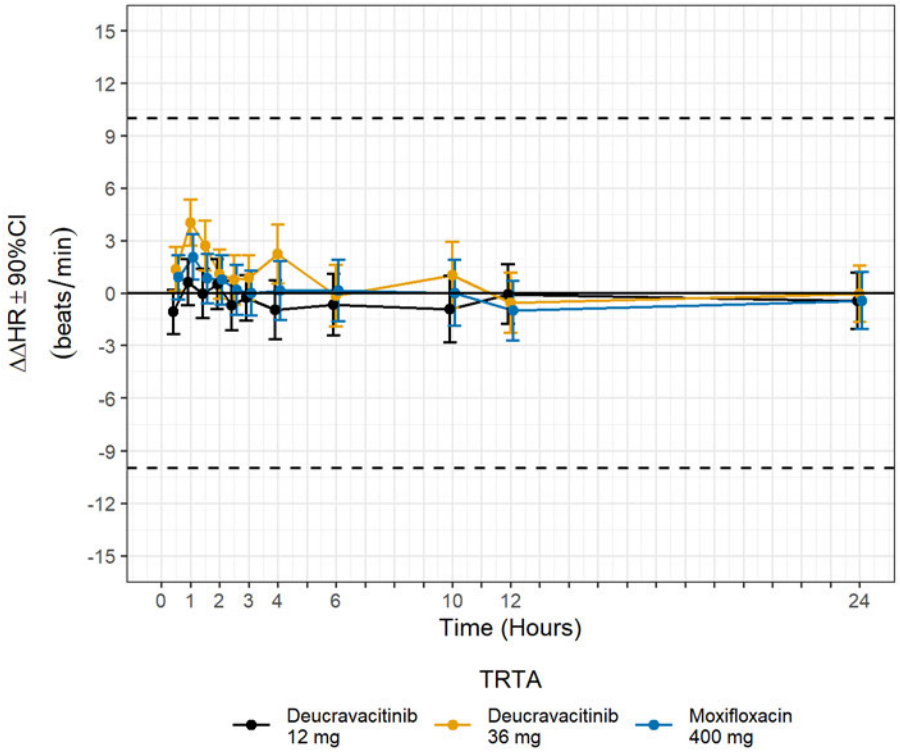
Table 3: The Point Estimates and the 90% CIs Corresponding to the Largest Lower Bounds for ΔΔQTcF

Treatment	N_{act}/N_{pbo}	Time (hours)	ΔΔQTCF (msec)	90.0% CI (msec)	97.5% CI (msec)
Moxifloxacin 400 mg	40/39	2.0	13.0	(11.3 to 14.6)	(10.7 to 15.2)

4.3.2 HR

Figure 2 displays the time profile of ΔΔHR for different treatment groups.

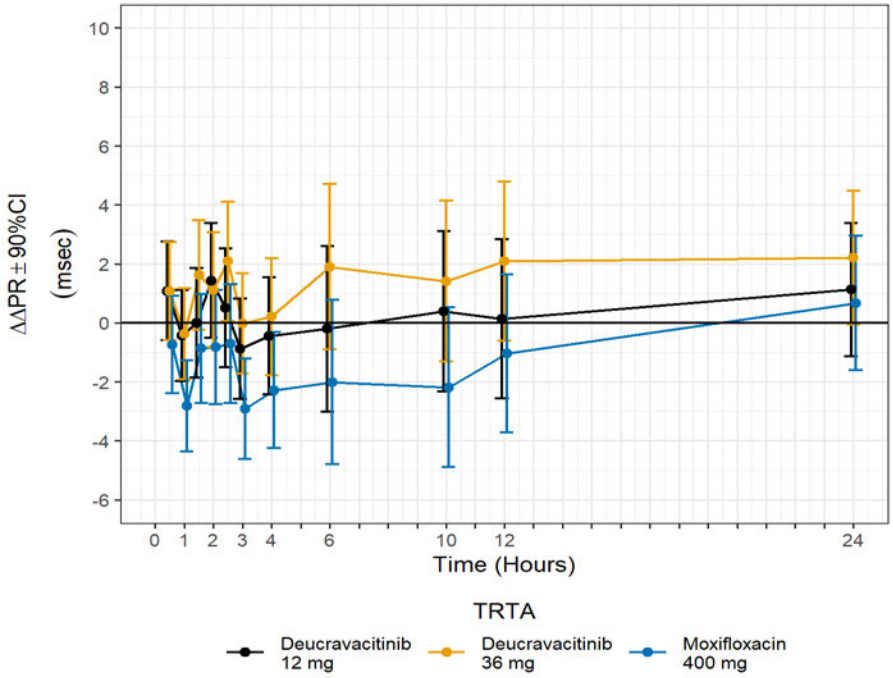
Figure 2: Mean and 90% CI of ΔΔHR Time-course



4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for different treatment groups.

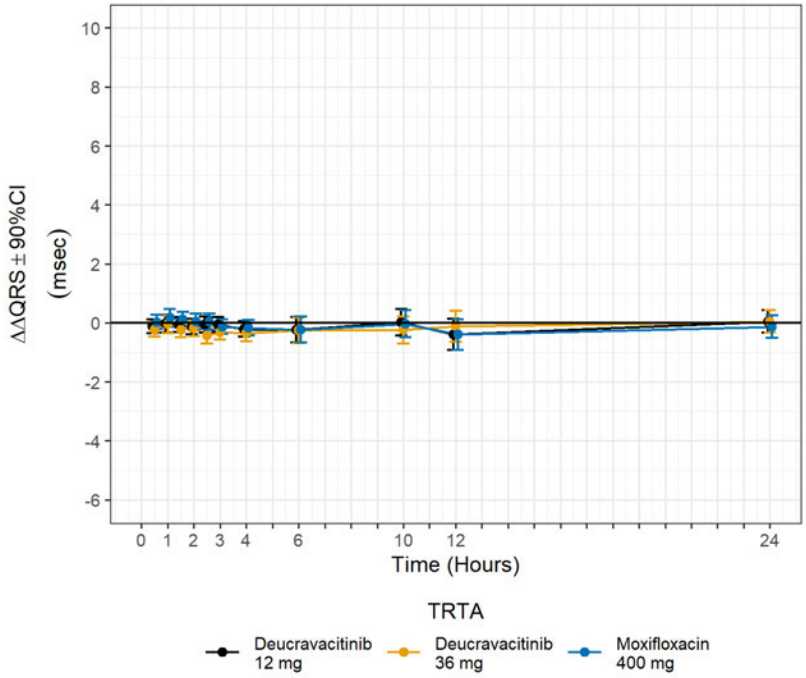
Figure 3: Mean and 90% CI of ΔΔPR Time-course



4.3.4 QRS

Figure 4 displays the time profile of ΔΔQRS for different treatment groups.

Figure 4: Mean and 90% CI of ΔΔQRS Time-course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs. In the following categorical tables, an omitted category means that no subjects had values in that category.

4.4.1 QTc

None of the subjects has QTcF value >450 msec. None of the subjects has ΔQTcF value >30 msec.

4.4.2 HR

None of the subjects has HR value >100 beats/min or <45 beats/min.

4.4.3 PR

None of the subjects has PR value >220 msec and 25% over baseline.

4.4.4 QRS

None of the subjects has QRS value >120 msec and 25% over baseline.

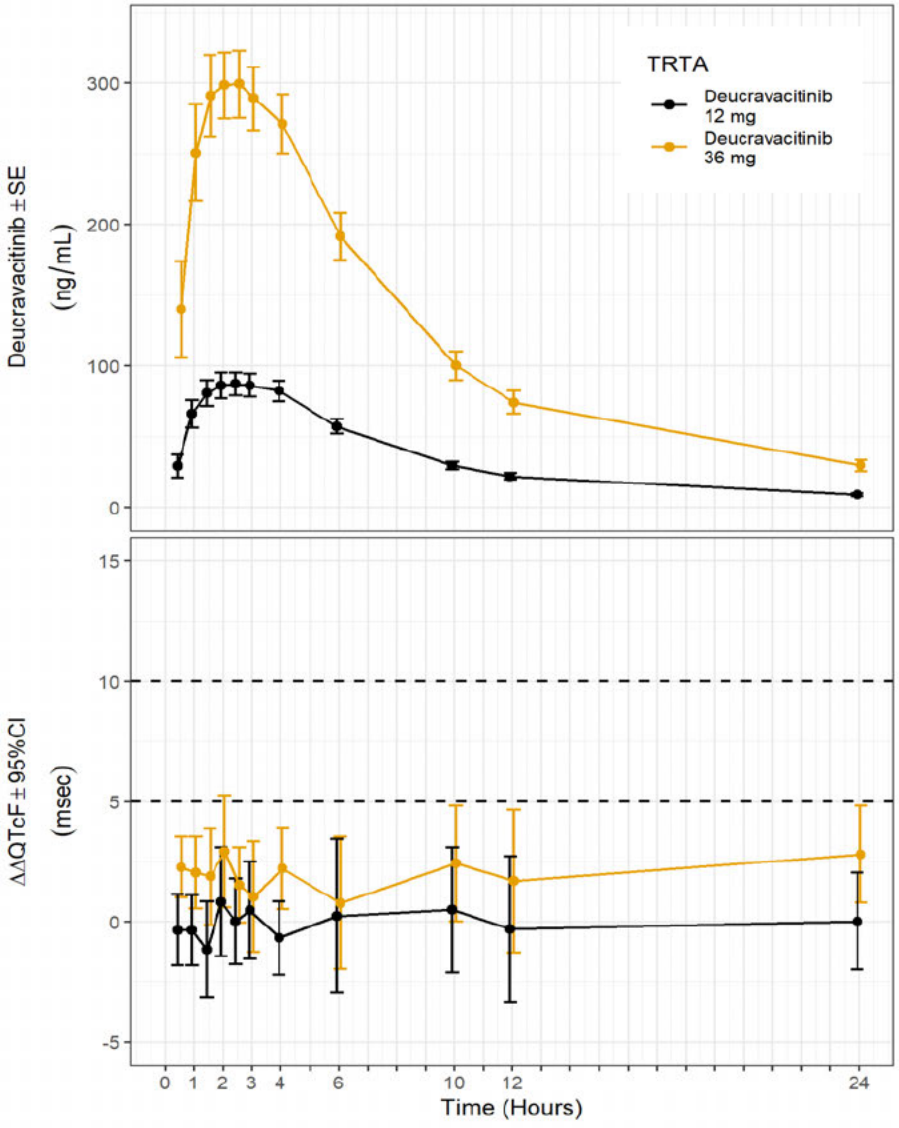
4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis was to assess the relationship between plasma concentration of deucravacitinib and ΔQTcF. Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG with time-matched PK.

Prior to evaluating the relationship between deucravacitinib concentration and QTc using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: absence of - 1) significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between deucravacitinib concentration and ΔQTc and 3) a non-linear relationship.

An evaluation of the time-course of deucravacitinib concentration and changes in ΔΔQTcF is shown in Figure 5. There was no apparent correlation between the time at maximum effect on ΔQTcF and peak concentrations of deucravacitinib indicating no significant hysteresis. Figure 2 shows the time-course of ΔΔHR, which shows an absence of significant ΔΔHR changes and the maximum change in heart rate is below 6 bpm (Sections 4.3.2 and 4.4.2).

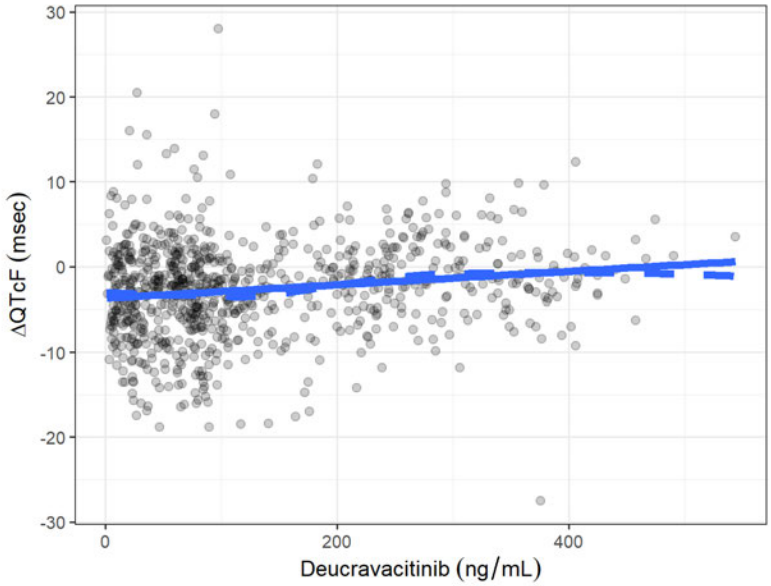
Figure 5: Time-course of deucravacitinib Concentration (top) and QTcF (bottom)[1]



After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between deucravacitinib concentration and ΔQTcF was evaluated to determine if a linear model would be appropriate. Figure 6 shows the relationship between deucravacitinib concentration and ΔΔQTc and supports the use of a linear model.

[1] ΔΔQTcF shown were obtained via descriptive statistics and might differ from Figure 1

Figure 6: Assessment of Linearity of the Concentration-QTcF Relationship



Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTcF model are provided in Table 4.

Figure 7: Goodness-of-fit Plot for QTcF

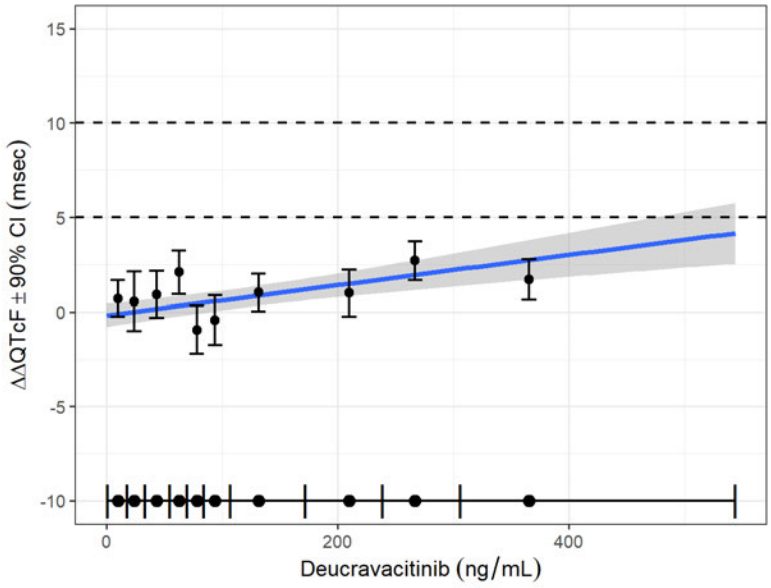


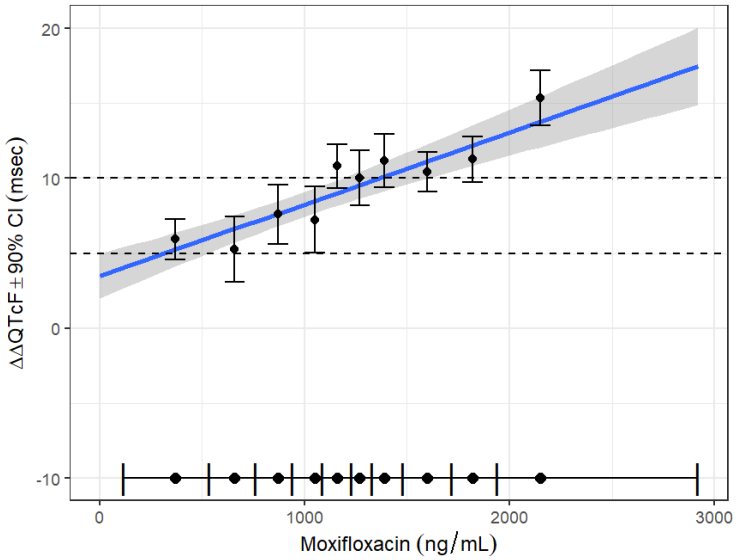
Table 4: Predictions from Concentration-QTcF Model

Actual Treatment	Analysis Nominal Period Day (C)	Deucravacitinib (ng/mL)	ΔΔQTcF (msec)	90.0% CI (msec)
Deucravacitin b 12 mg	1	91.9	0.6	(0.0 to 1.1)
Deucravacitin b 36 mg	1	314.6	2.3	(1.4 to 3.2)

4.5.1 Assay Sensitivity

To demonstrate assay sensitivity, the sponsor included oral moxifloxacin 400 mg as a positive control detecting small increases from baseline for QTcF in this study. The PK profile in the moxifloxacin group are generally consistent with the ascending, peak, and descending phases of historical data (*data not shown*). Concentration-response analysis of moxifloxacin data indicated a positive slope in the relationship between ΔQTcF and the plasma concentration of moxifloxacin. The lower limit of the two-sided 90% confidence interval at the observed mean peak concentrations of moxifloxacin is above 5 ms. Therefore, assay sensitivity is established.

Figure 8: Goodness-of-fit plot of ΔΔQTcF for Moxifloxacin



The goodness-of-fit plot for moxifloxacin is shown in Figure 8 and the predicted QTc at the geometric mean cmax is listed in Table 5.

Table 5: Predictions from Concentration-QTcF Model for Moxifloxacin

Actual Treatment	Analysis Nominal Period Day (C)	Moxifloxacin (ng/mL)	ΔΔQTcF (msec)	90.0% CI (msec)
Moxifloxacin 400 mg	1	1734.2	11.8	(10.5 to 13.0)

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/s/

GIRISH K BENDE
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RAMAN K BAWEJA
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Medical Officer's Review of NDA 214958
Ophthalmology Consultation

NDA 214958

Submission date: 9/10/2021
Consult Request: 3/ 8/2022
Review date: 3/21/2022

Sponsor: Bristol-Myers Squibb Company

Drug Name: Deucravacitinib

Indications: Psoriasis

Consult Request: On 9/10/2021, Bristol Myers Squibb Company submitted a new 505(b)(1) NDA 214958 deucravacitinib oral tablets. This is an NME that will be reviewed under the program. The proposed indication is treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. Deucravacitinib is a small molecule that inhibits tyrosine kinase 2 (TYK2). TYK2 is a JAK isoform that is required for signal transduction and cellular functions downstream of type I interferons (IFN), interleukin (IL)-23, and IL-12 which are involved in the initiation and pathogenesis of psoriatic disease. According to the Applicant, deucravacitinib achieves selective TYK2 inhibition by binding to the pseudokinase domain of TYK2 and locking the kinase in an inactive state. This binding site for deucravacitinib in the pseudokinase domain is separate and distinct from the kinase domain binding site for ATP-competitive JAK inhibitors.

There are 2 reported cases of retinal detachment related to the study drug treatment in the 2 Phase 3, 52-week, multi-center, randomized, double-blind, placebo- and active-controlled trials. We requested additional information regarding these cases and any others that may have been identified in other deucravacitinib development programs (link to Applicant's response, Question 4 under SDN 11). Retinal detachment is labeled for other JAK inhibitors (RINVOQ NDA 211675, CIBINQO NDA 213871) indicated for treatment of chronic inflammatory indications. The literature suggests that psoriasis is associated with retinal disease (Dai, Ying-Xiu et al. "Risk of retinal diseases in patients with psoriasis: A population-based cohort study in Taiwan." The Journal of dermatology vol. 48,10 (2021): 1550-1556.). However, in the Phase 3 studies retinal detachment was only reported in the treatment arm.

We request your help in evaluating the relevant information on the risk of retinal detachment related to the study drug treatment.

Response to Agency Inquiry

Request from Agency: Provide an assessment of cases of retinal detachment reported with deucravacitinib. A cumulative review of cases of retinal detachment associated with deucravacitinib use across all development programs must include a line listing and narrative of all cases, as well as an assessment of each case with the following information:

a. time to onset
b. pertinent clinical and diagnostic data
c. relevant medical history
d. concomitant medications
e. drug disposition
f. intervention(s) or treatment(s)
g. clinical outcome

Applicant Response:

A cumulative review of cases of retinal detachment reported with DEUC use across studies in the DEUC development program was performed. The list of the studies included in this search is provided in Appendix 1. To identify cases, AEs in clinical databases and listings up to 11-Feb-2022 were searched for preferred terms that included 'retinal detachment.'

The Phase 3 psoriasis studies in the NDA submission and the 120-day safety update (data cutoff date of 01-Oct-2021), included 1519 subjects exposed to DEUC for a total exposure of 2482.0 patient-years (Source: Day 120 Safety Update Report Table S.4.1.4). Among these subjects, two cases (2/1519; 0.131%) of retinal detachment were reported, resulting in an exposure-adjusted incidence rate (EAIR) of 0.1 per 100 patient-years (Source: Day 120 Safety Update Report Table S.5.4.4). The narratives for these cases are provided below.

There were no additional cases of retinal detachment reported among the approximately 1143 subjects exposed to DEUC at daily doses equal to or greater than proposed clinical dose of 6 mg QD for up to approximately 130 weeks across other studies in the DEUC development program. These studies include Phase 3 psoriasis studies conducted in Asia (b) (4) a Phase 2 study in psoriasis, and studies in other indications including psoriatic arthritis, systemic lupus erythematosus, lupus nephritis, discoid and/or subacute cutaneous lupus erythematosus, ulcerative colitis, and Crohn's disease.

The two cases of retinal detachment in the DEUC development program occurred in subjects in the IM011046 and IM011047 studies, the pivotal Phase 3 studies of DEUC in moderate-to-severe psoriasis.

Patient Identifier: IM011046-(b) (6) (Long-term extension study identifier: IM011075-(b) (6))			
Study Medication/Dose: IM011046: DEUC 6 mg QD Day1 ((b) (6)) - Day 363 ((b) (6)) IM011075: Day 364 ((b) (6)) - ongoing in long-term extension study as of (b) (6)			
Age: 43 YEARS	**Gender:** MALE	**Race:** ASIAN	**Ethnicity:** NOT HISPANIC/LATINO
Indication for Investigational Product: MODERATE TO SEVERE PLAQUE PSORIASIS			
Adverse Event (Preferred Term): Serous retinal detachment			

Clinical Summary:
Subject IM011046-(b) (6) was a 43-year-old male receiving DEUC 6 mg QD for psoriasis, with a medical history of gout (since (b) (6)) and hypertension (since (b) (6)). Concomitant medications included loxoprofen and telmisartan/amlodipine. On Day 244 ((b) (6)), the subject developed serous retinal detachment associated with visual impairment. Work up included visual acuity test on Day 251 ((b) (6)) with the finding of vision with correction both eyes 1.2, and Fundoscopy on Day 251 ((b) (6)) which revealed a serous retinal detachment in the right eye. On Day 282 ((b) (6)), the visual acuity test was repeated with the same result, vision with correction both eyes 1.2, and repeat of fundoscopy on this same day (Day 282, (b) (6)) revealed serous retinal detachment almost disappeared. No specific treatment was administered for the event. Study drug was continued without interruption. The event was reported by the investigator as being mild in severity, non-serious, and not related to study drug. The subject entered the long-term extension study (IM011075) on Day 364 ((b) (6)). During the long-term extension study, follow-up ophthalmologic tests were performed. On Day 372 of cumulative DEUC treatment ((b) (6)), fundoscopy showed "serous retinal detachment disappeared"; tonometry showed right eye 19.8, left eye 18.3; slit lamp microscopy (anterior eye) was within normal limits; and optical coherence tomography results stated, "serous retinal detachment disappeared". On Day 555 ((b) (6)), visual acuity test showed vision with correction both eyes 2.1; fundoscopy showed "serous retinal detachment no recurrence"; tonometry showed right eye 19.5, left eye 16.0; slit lamp microscopy (anterior eye) was within normal limits; and optical coherence tomography results stated "serous retinal detachment disappeared." The subject remains ongoing in the long-term extension study with no further eye-related events.

Reviewer's Comments: *Serous retinal detachments are distinctly different than rhegmatogenous retinal detachments. Serous retinal detachments, also known as retinal pigment epithelial detachments (RPED) occur primarily in men with a type-A personality under stress. As described in this case, they are single site, unilateral detachments best observable on optical coherent tomography. RPED which are drug related are usually bilateral and multifocal. This serous retinal detachment is not likely to be drug related.*

Second Case:

Patient Identifier: IM011047-(b) (6) (Long-term extension study identifier: IM011075-(b) (6))

Study Medication/Dose:
IM011047 Placebo Day 1 ((b) (6)) - Day 113 ((b) (6)); DEUC 6 mg QD Day 114 ((b) (6)) - Day 399 ((b) (6)) IM011075: Day 400 ((b) (6)) - ongoing in long-term extension study as of (b) (6)

Age: 53 YEARS	**Gender:** FEMALE	**Race:** BLACK or AFRICAN AMERICAN	**Ethnicity:** NOT HISPANIC

Indication for Investigational Product: MODERATE TO SEVERE PLAQUE PSORIASIS

Adverse Event (Preferred Term): Retinal detachment

Clinical Summary:
Subject IM011047-(b) (6) was a 53-year old female receiving DEUC 6 mg QD for psoriasis, with a medical history of hypertension (since (b) (6)), hypothyroidism (since (b) (6)) and total thyroidectomy ((b) (6)). Concomitant medications included amlodipine (since (b) (6))

and levothyroxine (since (b) (6)). BMI was 31.1 kg/m^2. On Day 365 ((b) (6)) in the IM011047 study, the subject was reported to have an SAE of retinal detachment. On the same day, ophthalmologic examination showed multiple breaks leading to retinal detachment in the left eye, and the subject underwent outpatient retinal detachment repair surgery to resolve the retinal detachment. Postoperatively, she was treated with difluprednate eye drops and neomycin/polymyxin-B/dexamethasone eye drops. The event was considered resolved on Day 365 ((b) (6)). The event was reported by the investigator as being severe in severity, serious, and not related to study drug. The event was considered by the investigator to be serious because it was an important medical event. Etiology and medical records specific to this event were requested from the site, but not received. On Day 400 ((b) (6)), the subject completed the IM011047 study and entered the long-term extension study (IM011075). The subject remains ongoing in the long-term extension study with no further eye-related events.

Reviewer's Comments: *Retinal detachments in patients over the age of 50 are not rare events. It is most common is individual with high degrees of myopia. The refractive error of this individual is not known.*

All Reported Ocular Adverse Events

Adverse Events, Controlled Safety Pool Week 0 though Week 16

	DEUC 6 mg qd	Placebo	Apremilast
	N=842	N=419	N=422
Eye Disorders	7(1%)	4 (1%)	2 (0.5%)
Dry Eye	2	0	0
Allergic Conjunctivitis	1	2 (0.5%)	0
Ocular Inflammation	1	0	0
Ocular Pruritus	1	0	0
Eye Swelling	1	0	0
Lacrimation Increased	1	0	0
Blurred Vision	1	0	2 (0.5%)
Cataract	0	1	0
Corneal Erosion	0	1	0

Adverse Event Summary, Controlled Safety Pool, Week 0 through Week 52

	DEUC 6 mg qd	Placebo	Apremilast
	N=1364	N=666	N=422
Eye disorders	29	4	4
Conjunctivitis allergic	4	1	0
Dry eye	4	0	0
Chalazion	3	0	0
Eye pruritus	3	0	0
Cataract	2	1	0
Eye irritation	2	0	0
Eye swelling	2	0	0
Vision blurred	2	0	2
Asthenopia	1	0	0
Astigmatism	1	0	0
Blepharitis	1	0	0
Eczema eyelids	1	0	0
Eye disorder	1	0	0

Eye Inflammation	1	0	0
Lacrimation increased	1	0	0
Myopia	1	0	0
Presbyopia	1	0	0
Refraction disorder	1	0	0
Retinal detachment	1	0	0
Serous retinal detachment	1	0	0
Vitreous loss	1	0	0
Conjunctival haemorrhage	1	0	1
Corneal erosion	0	1	0
Eye allergy	0	1	0
Eyelid oedema	0	0	1

Phase 3 Safety Pool: Week 0 (Parent Study) through IM011075 Safety Data Cutoff Date

BMS-986165 6 mg QD N=1519

	Events (N=1519)	%
Eye disorders	40	2.6
Conjunctivitis allergic	5	0.3
Dry eye	4	0.3
Cataract	3	0.2
Chalazion	3	0.2
Eye pruritus	3	0.2
Myopia	3	0.2
Blepharitis	2	0.1
Eye inflammation	2	0.1
Eye irritation	2	0.1
Eye swelling	2	0.1
Vision blurred	2	0.1
Asthenopia	1	0.1
Astigmatism	1	0.1
Conjunctival deposit	1	0.1
Diplopia	1	0.1
Dry age-related macular degeneration	1	0.1
Eczema eyelids	1	0.1
Erythema of eyelid	1	0.1
Eye disorder	1	0.1
Glaucoma	1	0.1
Lacrimation increased	1	0.1
Posterior capsule opacification	1	0.1
Presbyopia	1	0.1
Refraction disorder	1	0.1
Retinal detachment	1	0.1
Retinoschisis	1	0.1
Serous retinal detachment	1	0.1
Visual impairment	1	0.1
Vitreous degeneration	1	0.1
Vitreous detachment	1	0.1
Vitreous loss	1	0.1

Reviewer's Comments: *There is no apparent pattern of reported ocular adverse events.*

Summary Comments:

1. The two cases reported as retinal detachments are distinctly different types of events from each other. One case should more appropriately be labeled a central serous retinal pigment epithelial (RPE) detachment. While some RPE detachments are drug related, the reported features of this event are not consistent with drug related cases. Drug related cases are multifocal and bilateral. This case is unifocal and unilateral.

2. Rhegmatogenous retinal detachments are commonly associated with high myopia in older individuals. While the refractive error of the individual who had the rhegmatogenous retinal detachment is not known, the likelihood of this case being drug related is very low.

3. Review of all other ocularly reported adverse events did not suggest a pattern of reported ocular adverse events.

Wiley A. Chambers, MD
Supervisory Physician, Ophthalmology

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/s/

WILEY A CHAMBERS
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 9, 2022
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 214958
Product Name, Dosage Form, and Strength:	deucravacitinib tablet, 6 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Bristol-Myers Squibb Company
FDA Received Date:	September 10, 2021 and December 1, 2021
OSE RCM #:	2021-1817
DMEPA 1 Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA 1 Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 REASON FOR REVIEW

As part of the approval process for deucravacitinib tablet, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed deucravacitinib prescribing information (PI), patient package insert (PPI), container label, and professional sample labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the Prescribing Information (PI), Patient Package Insert (PPI), container labels, and carton labeling. We find the container label and professional sample labeling can be improved to facilitate product identification (e.g. adding linear barcode to container label), prevent administration errors [e.g. adding route of administration, increase prominence of strength], and prevent deteriorated drug errors (Lot and Expiration date placeholders). On some labels and labeling, we also note the use of the proposed proprietary name, (b) (4) *** which we found unacceptable due to orthographic similarity with another product[a]. We find the labels and labeling can be improved by using the placeholder "TRADENAME" until a new name is found to be conditionally acceptable. We recommend the placeholder, "TRADENAME" be

[a] Patel, M. Proprietary Name Review Memo for (b) (4) *** (NDA 214958). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 NOV 10. PNR ID. 2021-1044724190.

removed throughout the labels and labeling once a new name is found conditionally acceptable[b].

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed label and labeling can be improved and we provided recommendations below in Section 4.1 for the Division and Section 4.2 for the Applicant to address our concerns.

4.1 RECOMMENDATIONS FOR DIVISION OF DERMATOLOGY AND DENTISTRY (DDD)

A. General Comments

1. We recommend the placeholder, "TRADENAME" be removed throughout the labels and labeling once a new name is found conditionally acceptable.

4.2 RECOMMENDATIONS FOR BRISTOL-MYERS SQUIBB COMPANY

We recommend the following be implemented prior to approval of this NDA:

A. General Comments

1. The proposed proprietary name, (b) (4)***, used throughout the container labels, was found unacceptable by DMEPA under NDA 214958 on November 10, 2021 due to orthographic similarity with another product. Remove the proposed proprietary name, (b) (4)***, throughout the container labels and carton labeling. Until a new name is found to be conditionally acceptable, the placeholder, "TRADENAME" may be used. Once a proprietary name is found conditionally acceptable, the placeholder "Tradename" must be replaced with the proprietary name on the container labels and carton labeling and the revised labels and labeling must be submitted to the Agency for review.
2. As currently presented the placement of the semi-circle graphic close to the proprietary name is prominent. Placement of the graphic in front of the first letter in the proprietary name competes with readability of the proprietary name, which may lead to misinterpretation of the proprietary name. Thus, we recommend moving or removing this graphic.
3. We recommend adding the route of administration "for oral use" to the principal display panel (PDP), as per Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013.
4. For the professional sample, increase the prominence of the strength. The strength presentation should be more prominent than the net quantity statement.

[b] The Applicant submitted proposed proprietary name, Sotyktu*** on February 1, 2022. The proprietary name, Sotyktu*** is pending with the user fee goal date of May 2, 2022.

5. As currently presented for the commercial size container label, we did not identify a placeholder for the linear barcode for the product other than the one labeled for position. Please note, the drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible. Therefore, we request you add the product's linear barcode to each individual container as required per 21CFR 201.25(c)(2).
6. As currently presented, we did not identify a placeholder ("LOT" or "EXP") for the lot number and expiration date on the proposed carton labeling. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
7. Additionally, in September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.[1] The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. The human-readable product identifier contains the NDC, serial number, lot, and expiration date. The DSCSA guidance on product identifiers recommends the format below for the human-readable portion of the product identifier. The guidance also recommends that the human-readable portion be located near the 2D data matrix barcode.

    NDC: [insert product' s NDC]
    SERIAL: [insert product' s serial number]
    LOT: [insert product' s lot number]
    EXP: [insert product' s expiration date]

[1] The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for deucravacitinib received on December 1, 2021 from Bristol-Myers Squibb Company.

Table 2. Relevant Product Information for deucravacitinib

Initial Approval Date	N/A
Active Ingredient	deucravacitinib
Indication	treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy
Route of Administration	oral
Dosage Form	tablet
Strength	6 mg
Dose and Frequency	6 mg taken orally once daily, with or without food. Do not crush, cut, or chew the tablets
How Supplied	<table><tr><th>Tablet Strength</th><th>Tablet Color/Shape</th><th>Tablet Markings</th><th>Package Size</th><th>NDC Code</th></tr><tr><td>6 mg</td><td>Pink round, biconvex, film-coated tablet</td><td>Laser printed with "BMS 895" and "6 mg" on one side (b) (4) (b) (4)</td><td>Bottles of 30</td><td>0003-0895-11</td></tr></table>
Storage	20° to 25°C (68° to 77°F); excursions permitted between 15° and 30°C (59° and 86°F).
Container Closure	Bottle, blister-card wallet (professional sample)

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following deucravacitinib labels and labeling submitted by Bristol-Myers Squibb Company.

- Container Label received on September 10, 2021
- Professional Sample Blistercards received on September 10, 2021
- Prescribing Information and Patient Package Insert (Image not shown) received on December 1, 2021, available from \\CDSESUB1\evsprod\nda214958\0005\m1\us\init-nda-pso-decru-pro.pdf

G.2 Label and Labeling Images

Container Label

4 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MADHURI R PATEL
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SEVAN H KOLEJIAN
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